

## ORIGINAL ARTICLE

# Head and neck cancer risk calculator (HaNC-RC)—V.2. Adjustments and addition of symptoms and social history factors

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## Abstract

**Objectives:** Head and neck cancer (HNC) diagnosis through the 2-week wait, urgent suspicion of cancer (USOC) pathway has failed to increase early cancer detection rates in the UK. A head and neck cancer risk calculator (HaNC-RC) has previously been designed to aid referral of high-risk patients to USOC clinics (predictive power: 77%). Our aim was to refine the HaNC-RC to increase its prediction potential.

**Design:** Following sample size calculation, prospective data collection and statistical analysis of referral criteria and outcomes.

**Setting:** Large tertiary care cancer centre in Scotland.

**Participants:** 3531 new patients seen in routine, urgent and USOC head and neck (HaN) clinics.

**Main outcome measures:** Data collected were as follows: demographics, social history, presenting symptoms and signs and HNC diagnosis. Univariate and multivariate regression analysis were performed to identify significant predictors of HNC. Internal validation was performed using 1000 sample bootstrapping to estimate model diagnostics included the area under the receiver operator curve (AUC), sensitivity and specificity.

**Results:** The updated version of the risk calculator (HaNC-RC v.2) includes age, gender, unintentional weight loss, smoking, alcohol, positive and negative symptoms and signs of HNC. It has achieved an AUC of 88.6% with two recommended triage referral cut-offs to USOC (cut-off: 7.1%; sensitivity: 85%, specificity: 78.3%) or urgent clinics (cut-off: 2.2%; sensitivity: 97.1%; specificity of 52.9%). This could redistribute cancer detection through USOC clinics from the current 60.9%–85.2%, without affecting total numbers seen in each clinical setting.

**Conclusions:** The use of the HaNC-RC v.2 has a significant potential in both identifying patients at high risk of HNC early through USOC clinics but also improving health service delivery practices by reducing the number of inappropriately urgent referrals.

## 1 | INTRODUCTION

The cancer treatment outcomes in the UK have been persistently lower than many countries in Europe as has been highlighted in the EURO CARE cancer studies.<sup>1,2</sup> It has been suggested that this may be due to the delays in cancer detection, with patients presenting in advanced cancer stages.<sup>3</sup> Head and neck cancer (HNC) is the 8th most common cancer in the UK with a continuing rise in its incidence.<sup>4</sup> Previous audits from England and Ireland showed that the majority of cancers are diagnosed at a disease stage III or IV.<sup>4,5</sup> 21% of HNC patients visited their GP more than twice prior to being diagnosed with cancer.<sup>6</sup>

In the recent years, there has been a drive for the development of risk calculators designed to identify cancer at early stages. This is an area of great opportunity for improvement of patients' cancer journeys from initial presentation in primary care, to diagnosis in the hospital setting and initiation of treatment.<sup>7</sup> At present, several risk calculators are available for common cancers, such as prostate, lung or ovarian cancer, which have been externally validated and are recommended for use to aid prompt referral of high-risk individuals to specialist clinics for further assessment.<sup>8</sup> However, most of these normograms require results of blood tests and radiological findings—in addition to patients' symptoms and demographics—to calculate cancer probability, which potentially limits their widespread adoption in the primary care settings.<sup>9</sup> On the other hand, there are also examples where risk can be established solely on the basis of symptoms and demographics, such as for lung and colorectal cancer.<sup>10-12</sup>

Risk calculators do not only have the potential to contribute to earlier diagnosis of cancers but could also lead to service delivery improvements. Only 35%-38% of HNC in the UK are currently diagnosed via the 2-week wait pathway, with the rest of cases identified in other types of outpatient appointments or emergency admissions.<sup>13</sup> With an average of 100 000 HNC urgent suspicion of cancer (USOC) referrals annually in the UK<sup>14</sup> and an annual HNC incidence of 12 000,<sup>4</sup> one can extrapolate a UK-wide USOC HNC conversion rate of 4.3%. A review of the literature has highlighted a large number of inappropriate USOC referrals and an average HNC diagnosis of only 8%.<sup>15,16</sup>

The above underline the importance of early HNC diagnosis and the need for change of the current referral pathways. Although cancer risk calculators have been available for the last 10-20 years for other common cancers, prediction models for HNC have only recently started to emerge. The first head and neck cancer risk calculator (HaNC-RC) in 2016 based on patients' symptoms, signs and demographics using data from 4715 patients seen in USOC clinics from Birmingham and Newcastle (area under the receiver operator characteristic curve [AUC]: 0.77; sensitivity: 74.8%, specificity: 65.9%).<sup>16</sup> The variables included in the model are available in Table 1. It was subsequently externally validated with a cohort from a different UK region (Glasgow), yielding an AUC of 0.81, combined with high sensitivity (79.3%) and specificity (68.6%).<sup>17</sup> Another calculator was proposed by a different research group, applying an alternative symptom combination, demographics as well as smoking and alcohol

### Keypoints

- The majority of head and neck cancers (HNC) in the UK are diagnosed via non urgent suspicion of cancer (USOC) routes.
- A head and neck cancer risk calculator was created in 2016 to identify individuals at high risk of HNC for a USOC referral.
- The calculator is now updated (HaNC-RC v.2) with inclusion of social history factors, further significant symptoms and refinement of previously included symptoms.
- HaNC-RC v.2 has a higher predictive power; sensitivity and specificity compared with its previous version.
- It is envisaged that the HaNC-RC v2 will be used to effectively triage patients to routine, urgent and USOC clinics to reduce cancer waiting times and increase HNC diagnosis through the USOC pathway.

data based on a cohort of 1075 USOC referrals (Table 1). Although the AUC was high at 0.79, the sensitivity was low at 31% with high false negative figures in their external validation cohort.<sup>18</sup> Artificial intelligence methods have also been attempted for the development of HNC risk calculators with the variation logistic regression being suggested the most effective method.<sup>19</sup> (Table 1).

Current trends in this area lean towards validation of existing normograms, combined with continuous improvement through further iterations for increased predictive power instead of continuous generation of new prediction models.<sup>20</sup> The aim of this study was therefore to attempt to further increase the predictive power of the HaNC-RC by assessing the potential for inclusion of other significant symptoms (such as weight loss, neck pain and sore throat), the refinement of symptoms already in the model (addition of symptom laterality and persistency) and the addition of social history factors (smoking, alcohol).

## 2 | METHODS

Data were collected prospectively from new patients seen in all types of head and neck (HaN) clinics (USOC, urgent, routine) from January 2017 until December 2018 in hospitals covering the Greater Glasgow and Clyde region. Sample size calculation indicated that assuming the lowest estimated disease prevalence which currently sits at 8% amongst symptomatic individuals referred by their GP to suspicion of cancer clinics, to demonstrate test performance of at least 80% sensitivity and 75% specificity to within  $\pm 5\%$  with 80% power. The sample was initially collected on all referrals, but after the first 18 months of data collection, the cancer incidence was lower than the expected 8% (aiming for >300 cancer cases) whilst reaching saturation of the non-cancer referrals symptoms. Hence data collection continued only for

**TABLE 1** Suggested models for triaging of HNC referrals

Publication	Variables	Model statistics
Tikka et al, 2016	Age	Model build: Logistic regression
	Gender	Population: USOC referrals
	Persistent hoarseness >3 wk	Sensitivity: 74.8%
	Oral ulcer >3 wk	Specificity: 65.9%
	Oral swelling >3 wk	AUC: 0.77
	Persistent dysphagia >3 wk	Probability Cut-off: 8%
	Neck lump >3 wk	External validation
	Haemoptysis	AUC: 0.81
	Feeling of lump in throat	Sensitivity: 79.3%
	Recent unexplained neck lump (<3 wk)	Specificity: 68.6%
	Unexplained otalgia	
	Intermittent hoarseness	
	Odynophagia	
Lau et al, 2018	Age	Model build: Logistic regression
	Smoking pack years	Population: USOC referrals
	Alcohol units over RWI	Sensitivity: 31%
	Oral ulcer	Specificity: 92%
	Neck lump	AUC: 0.79
	Ear lesion	Probability cut-off: not mentioned
	Facial lesion	
	Tongue ulcer	
	Weight loss	
	Unilateral hearing loss	External validation: Not performed
	Thyroid swelling	
Moor et al, 2019	Variables included not mentioned	Model build: Different machine learning techniques. Population: USOC referrals Best performance: Variational logistic regression True negative rate (specificity): 25.8 ± 8.9 False negative rate: 0.1 ± 0.16 False positive rate: 66.4 ± 8.9 True positive rate (sensitivity): 7.7 ± 1.4 AUC, probability thresholds, sensitivity, specificity: Not mentioned External validation: No

patients with a cancer diagnosis until the targeted number of cancer cases was reached ( $n = 77$  additional cancer cases), in order to boost cancer numbers to enable better prediction using logistic regression analysis modelling. This resulted in a total number of 3531 cases and 307 cancers, with no missing data, for statistical analysis. The HNC incidence, cancer diagnosis per clinic appointment, calculation of negative predictive value (NPV), positive predictive value (PPV) and suggested re-triaging following the risk calculator development were calculated in the un-boosted cancer cohort to ensure non-contamination of sample from cancer boosting. Table 2 summarised the data collection proforma. The HNC diagnosis included all primary cancers to the HaN regions

( $n = 247$ ), metastatic cancers to the HaN from other regions, including lymphoma ( $n = 48$ ) and cancers in neighbouring regions that manifested with HaN symptoms ( $n = 12$ ).

## 2.1 | Statistical analysis

Univariable logistic regression analysis was performed to identify significant variables for potential inclusion in the multivariate analysis. All variables that reached the  $\alpha = .1$  level of significance were screened for potential inclusion including any possible two-way interactions of these variables which met the stricter threshold for

**TABLE 2** Pre-agreed data collection proforma

Data collection proforma
Age
Gender (male, female)
Smoking (current, ex-smoker, non-smoker)
Alcohol (>14 unit/week, ≤14 units/week, previous excess)
Unintentional weight loss
Any presenting symptoms with mention of duration, laterality, persistency
Any presenting signs (findings during examination of neck with palpation, examination of oral cavity and oropharynx with head light and tongue depressor and inspection of skin of head and neck for any lesions including anterior rhinoscopy with a nasal speculum)—flexible endoscopy finding not included.

inclusion using the Bonferroni correction ( $\alpha = .1/\text{number of interactions tested}$ ). Backwards elimination was undertaken to identify a parsimonious model with each of the finally included variables having a  $P$  value of  $\alpha = .05$  or less. Internal validation of the final model was performed using 1000 bootstrap samples each performing random splits of the data set into training and validation sets with a final generation of the estimated mean AUC across each of the 1000 validation sets. The suggested probability cut-off for a USOC referral was selected to be the probability value that generated the highest value combination of sensitivity and specificity simultaneously. Following exclusion of the USOC cases, a second threshold was calculated using the same principle for the rest of the referrals, with those above the recommended cut-off being considered for an urgent (6 weeks) appointment. Chi-square

analysis was performed to compare the distribution of HNC diagnosis based on the current GP triaging and the one generated implementing the USOC and urgent thresholds on our data set. For the reclassification of referrals, the true incidence of cases was used; hence, the un-boosted cancer cases were used ( $n = 230$ ) and for the calculation of the NPV and PPV based on the USOC cut-off. AUC, sensitivity and specificity values were also calculated using the previous version of the HaNC-RC for comparisons to the latest version. The R and SPSS statistical software were used for data analysis. The R libraries used for prediction and AUC were as follows: Epi; ROCR; Deducer.

## 2.2 | Ethical considerations

The data reported by the clinicians in the clinical notes did not deviate from standard practice. No ethics committee approval was therefore required for this study. Instead, the project was registered with Caldicott guardian of the NHS Greater Glasgow and Clyde (GGC/07/02/17) as quality improvement project. No patient identifiable information was included in the database.

## 3 | RESULTS

The data set included a total of 3650 patients seen in HNC clinics during the 18 months period. There were missing data for 119 patients who were excluded from any further analysis. 1067 (30.2%) of the 3531 patients were referred in the USOC clinics. 307 (8.7%) patients were diagnosed with HNC but only 59.9% of these were

	Head and neck cancer		OR (95% CI)	P value *
	Yes	No		
Gender				
Males	208 (14.3%)	1246 (85.7%)	3.34 (2.6-4.9)	.0001
Females	99 (4.8%)	1978 (95.2%)		
Age				
Mean (SD)	63.7 (9.1)	57 (16.9)	1.03 (1.02-1.03)	.0001
Smoking				
Current	145 (16.3%)	744 (83.7%)	Current vs never: 3.8 (2.9-5.1)	.0001
Ex	85 (8.1%)	963 (91.9%)	Ex vs never: 1.7 (1.3-2.4)	
Never	77 (4.8%)	1517 (95.2%)		
Alcohol				
>14 units/week	85 (20.6%)	327 (79.4%)	>14 u/w vs ≤14 u/w: 5.4 (3.4-8.3)	.001
Previous excess	30 (26.8%)	82 (73.2%)	Ex excess vs ≤14u/w: 3.8 (2.9-5.0)	
≤14 units/week	192 (6.4%)	2815 (93.6%)		

**TABLE 3** Patients demographics, smoking and alcohol as risks factors for head and neck cancer

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Univariable binary logistic regression.

**TABLE 4** Patient presenting complaints and symptoms

	Head and neck cancer		P value*
	Yes	No	
<b>Unintentional weight loss</b>			
Yes	71 (25.7%)	205 (74.3%)	.0001
No	236 (7.3%)	3019 (92.7%)	
<b>Hoarseness</b>			
Persistent	75 (20.1%)	299 (79.9%)	.0001
Intermittent	13 (1.9%)	655 (98.1%)	
Persistent explained (after URTI/stroke/surgery/voice use excess at work or hobby)	3 (3.7%)	79 (96.3%)	
No	216 (9%)	2191 (91%)	
<b>Sore throat</b>			
Persistent bilateral/midline	32 (20.9%)	121 (79.1%)	.0001
Persistent unilateral	24 (53.3%)	21 (46.7%)	
Intermittent bilateral/midline	3 (1.3%)	98.7%	
Intermittent unilateral	1 (4.3%)	22 (95.7%)	
No	247 (8%)	2825 (92%)	
<b>Throat discomfort/irritation</b>			
Yes	16 (6.2%)	242 (93.8%)	.142
No	291 (8.9%)	2982 (91.1%)	
<b>Feeling of something in throat (FOSIT)</b>			
Yes	9 (1.5%)	578 (98.5%)	.0001
No	298 (10.1%)	2646 (89.9%)	
<b>Dysphagia</b>			
Persistent	70 (28.5%)	176 (71.5%)	.0001
Intermittent	4 (1.6%)	253 (98.4%)	
No	233 (7.7%)	2795 (92.3%)	
<b>Regurgitation</b>			
Yes	8 (7.5%)	99 (92.5%)	.650
No	299 (8.7%)	3125 (91.3%)	
<b>Odynophagia</b>			
Yes	38 (48.1%)	41 (51.9%)	.0001
No	269 (7.8%)	3183 (92.2%)	
<b>Neck pain</b>			
Persistent bilateral/midline	8 (16.7%)	40 (83.3%)	.364
Persistent unilateral	6 (10.5%)	51 (89.5%)	
Intermittent bilateral/midline	0	39 (100%)	
Intermittent unilateral	2 (5.4%)	35 (94.6%)	
No	291 (8.7%)	3059 (91.3%)	

(Continues)

**TABLE 4** (Continued)

	Head and neck cancer		P value*
	Yes	No	
<b>Neck lump</b>			
Persistent	144 (17.5%)	681 (82.5%)	.0001
Intermittent/regressing	8 (2.9%)	270 (97.1%)	
No	155 (6.4%)	2273 (93.6%)	
<b>Choking episodes/feeling</b>			
Yes	8 (4.5%)	168 (95.5%)	.05
No	299 (8.9%)	3056 (91.1%)	
<b>Catarrh/mucus</b>			
Yes	1 (0.7%)	135 (99.3%)	.01
No	306 (9%)	3089 (91%)	
<b>Blocked nose</b>			
Unilateral	0	8 (100%)	.999
Bilateral	0	22 (100%)	
No	307 (8.8%)	3194 (91.3%)	
<b>Oral swelling</b>			
Yes	55 (32.5%)	114 (67.5%)	.0001
No	252 (7.5%)	3110 (92.5%)	
<b>Oral ulcer</b>			
Yes	12 (48%)	13 (52%)	.0001
No	295 (8.4%)	2311 (91.6%)	
<b>Haemoptysis</b>			
Yes	11 (14.5%)	65 (85.5%)	.075
No	296 (8.6%)	3159 (91.4%)	
<b>Unexplained unilateral otalgia (normal otoscopy)</b>			
Yes	28 (29.2%)	68 (70.8%)	.0001
No	279 (8.1%)	3156 (91.9%)	
<b>Face pain/numbness</b>			
Yes	0	27 (100%)	.998
No	307 (8.7%)	3197 (91.2%)	
<b>Noisy breathing/stridor</b>			
Yes	6 (50%)	6 (50%)	.0001
No	301 (8.6%)	3218 (91.4%)	
<b>Red/white patch in mouth</b>			
Yes	2 (4.7%)	41 (95.3%)	.353
No	305 (8.7%)	3183 (91.3%)	
<b>Persistent head and neck skin lesion</b>			
Yes	8 (21.1%)	30 (78.9%)	.009
No	299 (8.6%)	3194 (91.4%)	

\*Univariable binary regression analysis

diagnosed through the USOC route. The HNC incidence (un-boosted cohort) was 6.66% (n = 230).

The majority of patients were female (n = 2077, 58.8%). The mean age was 57.2 (SD:16.8). 889 (25.2%) were current smokers. Alcohol was consumed in excess by 11.7% of patients (n = 412)

**TABLE 5** Multivariable binary logistic regression of the final selected model

Variable	Estimate	SE	P value	Odds ratio (95% CI)
Intercept	-6.890	0.433	<.0001	
Age	0.028	0.005	<.0001	1.029 (1.018-1.398)
Gender				
Male vs female	1.031	0.163	<.0001	2.805 (2.043-3.872)
Unintentional weight loss				
Yes vs no	0.778	0.228	.0006	2.178 (1.384-3.383)
Smoking				
Yes vs no	0.602	0.188	.0001	1.827 (1.265-2.645)
Ex vs no	0.360	0.191	.0588	1.434 (0.986-2.085)
Alcohol				
>14 units/week vs ≤14 units/week	0.753	0.194	.0001	2.123 (1.446-3.098)
Ex excess vs ≤14 units/week	0.545	0.313	.0814	1.725 (0.919-3.145)
Hoarseness				
Persistent vs no	1.813	0.227	<.0001	6.129 (3.942-9.593)
Intermittent vs no	-0.188	0.338	.5791	0.829 (0.408-1.556)
Explained persistent vs no	0.384	0.668	.5651	1.469 (0.315-4.682)
Sore throat				
Persistent bilateral/midline vs no	0.767	0.311	.0136	2.154 (1.152-3.907)
Persistent Unilateral vs no	2.269	0.489	<.0001	9.678 (3.671-25.069)
Intermittent bilateral/midline vs no	-1.124	0.614	.0670	0.325 (0.077-0.924)
Intermittent unilateral vs no	0.1501	1.114	.8929	1.162 (0.058-7.029)
FOSIT				
Yes vs no	-1.209	0.399	.0025	0.298 (0.127-0.615)
Dysphagia				
Persistent vs no	1.266	0.245	<.0001	3.547 (2.182-5.719)
Intermittent vs no	-1.206	0.574	.0357	0.299 (0.082-0.813)
Odynophagia				
Yes vs no	2.604	0.216	<.0001	13.522 (6.033-30.536)
Neck lump				
Persistent vs no	2.424	0.216	<.0001	11.288 (7.447-17.395)
Intermittent/regressing vs no	0.541	0.429	.2071	1.718 (0.691-3.785)
Oral swelling				
Yes vs no	2.251	0.267	<.0001	9.502 (5.631-16.071)
Oral ulcer				
Yes vs no	1.903	0.585	.0001	6.707 (2.107-20.995)
Unilateral otalgia with normal otoscopy				
Yes vs no	1.169	0.355	.0009	3.220 (1.588-6.401)
Stridor				
Yes vs no	2.307	0.914	.0116	10.049 (1.414-57.132)
Persistent head and neck skin lesion				
Yes vs no	2.193	0.475	<.0001	8.963 (3.358-22.0677)

Abbreviations: FOSIT, feeling of something in throat; SE, standard error.

using the UK government recommendation of 14 units of alcohol per week as the recommended limit. The significance of the above demographics in HNC diagnosis on univariable analysis is presented in Table 3.

The most common presenting symptom was hoarseness ( $n = 1124$ , 31.8%), followed by presence of a neck lump ( $n = 1103$ , 31.2%). Table 4 summarises presenting symptoms, sub-grouped for cancer diagnosis and the univariable logistic regression findings. All

**TABLE 6** Cancer detection in head and neck clinics with current triage system compared with suggested HaNC-RC v2 triaging (USOC referral: for probability cut-offs  $\geq 0.071$ , urgent referrals: probability cut-offs 0.022- 0.0709; routine referrals  $< 0.022$ )

	Current triaging pathway (GP referrals)			Suggested triaging (HaNC-RC v2)		
	Cancer			Cancer		
	Yes	No	Total	Yes	No	Total
Routine	30 (13%)	1339 (41.5%)	1369 (39.6%)	6 (2.6%)	1625 (50.4%)	1631 (47.2%)
Urgent	60 (26.1%)	1002 (31.1%)	1062 (30.7%)	28 (12.2%)	849 (26.3%)	877 (25.4%)
USOC	140 (60.9%)	883 (27.4%)	1023 (29.6%)	196 (85.2%)	750 (23.3%)	946 (27.4%)

Note: Data reflect true cancer incidence per clinic type from the un-boosted cancer population.

symptoms were present for at least 3 weeks. Multivariate regression analysis identified 12 symptoms as significant predictors of HNC. Patients' demographics, alcohol and smoking status were also significant factors. Table 5 shows the variables included in the new version of the HaNC-RC (v.2). None of the 2-way interactions reached the Bonferroni corrected threshold for significance. The predictive power of the model calculated by the area under the receiver operation curve (AUC) following internal validation was 0.8856; 95% CI: 0.8818-0.8879.

The 0.071 probability cut-off maximised sensitivity and specificity at the same time, and it is recommended as a cut-off point for referral of patients in the USOC (sensitivity: 85%, specificity: 78.3%). The PPV was 20.7%, and the NPV was 98.6%. For health-care systems that have a second clinic classification on 4 weeks urgency, a second cut-off was generated at 0.022 with a sensitivity of 97.1% and a specificity of 52.9% that maximised again sensitivity and specificity after cases of probability of more than .071 were excluded. Finally, the sensitivity and specificity results of the revised calculator were compared with the output of the previous version of the calculator using our current cohort. Applying the older version of the HaNC-RC, the sensitivity dropped by 5%-80.78% and specificity by 10%-68.08%, with an AUC of 0.801. Hence, a head to head comparison of the diagnostic power for the first and second version of the calculator showed improved sensitivity and specificity values.

We modelled the potential impact the calculator could have on patient referral. Table 5 shows how the HaNC-RC v.2 would have redistributed patients to clinics, including the resulting impact on cancer detection per clinic type. The calculations were based on the un-boosted cancer population. The data suggest that the number of patients diagnosed in clinics is significantly reduced from 39.1% (26.1% in urgent clinics; 13% in routine) to 14.8% (12.2% in urgent, 2.6% in routine) whilst the cancer detection from the USOC clinics would be significantly increased from 60.9% to 85.2%. The change in the cancer diagnosis using the HaNC-RC v2 re-triaging was statistically significant ( $P < .0001$ ), and this could occur whilst seeing less patients through the USOC and urgent route (Table 6).

An online calculator to measure the HNC probability of a patient presenting with the symptoms and signs of the HaNC-RC v2 is available online at <http://orlhealth.com/risk-calculator-2.html>.<sup>21</sup>

## 4 | DISCUSSION

### 4.1 | Synopsis of new findings

Our study increased the predictive power of the previous HaNC-RC (v.1) from 77%<sup>16</sup> to 88.6%. The HaNC-RC v.2 includes smoking (current, ex-smoker and non-smoker) and alcohol history (>14 units/week,  $\leq 14$  units/week, previous excess), data that were not available in the previous iteration of the calculator. We also included in the updated version new significant symptoms: sore throat (to include persistency and laterality), unintentional weight loss, stridor, HaN skin lesion, and we refined symptoms already in the risk calculator (hoarseness—accounting for persistency and previous relevant history, dysphagia and neck lump—to include persistency). By including intermittent/persistent and unilateral/bilateral-midline, we accounted for the varying presentation of common HaN symptoms.

The previous version of the calculator included significant interactions between negative and positive symptoms for cancer which did not significantly alter the prediction power of the calculator this time; hence, they were dropped from the revised model. This reflects the fact that stronger predictors are now included in the HaNC-RC v.2.

Our study has also demonstrated that it is possible for most HNC patients to be diagnosed through USOC clinics by triaging their referral using the HaN-RC v.2. The cancer detection in the USOC clinics could have increased from the current pick up rate of 60.9% to 85.2%, with only 2.6% of cancer having delayed detection in routine clinics compared with the current figure of 13%. With waiting times for a routine appointment currently being in the region of 3 months to up to more than 25 weeks in some regions,<sup>13,14</sup> this can translate in a significant reduction of the time from referral to cancer diagnosis. The improved figures could be obtained without increasing the number of patients seen in the USOC clinics.

### 4.2 | Comparison with other studies

The new variables included in the HaNC-RC v.2 are supported by previous cohort studies in the USOC referrals in which univariate

analysis was performed to identify significant cancer predictors such as unintentional weight loss, smoking and alcohol.<sup>16,17</sup> Persistent hoarseness and neck lump have been previously highlighted as the most common symptoms resulting in cancer diagnosis.<sup>16-19</sup> These symptoms were part of HaNC-RC since its first version. One of the new additions to the HaNC-RC v2 is the sore throat symptom. This is supported by recent studies, showing unilateral sore throat to have a 9.5% positive predictive value in identification of HNC.<sup>22</sup> Indeed, in our multivariate model, patients with unilateral persistent sore throat were 9.7 times more likely to have cancer compared with individuals without sore throat. By making these changes, the predictive power of the revised calculator, following internal validation, was 88.6%. This is substantially higher than the ROC of the HaN-RC v.1 (77%) and the ROC of the Lau et al, model (79%).<sup>16,18</sup>

Our study is the first to include patients from all types of clinic appointments, not just USOC referrals, to look for significant predictors of HNC. This has also allowed us to assess how many patients are diagnosed with cancer per clinic type and how re-triaging using the HaNC-RC v2 can improve this number. Triaging patients in the manner can result in a number needed to treat (NNT) of four to identify a cancer (25% cancer yield from USOC clinics), compared with the current average number of 12.5.<sup>15</sup>

The potential benefits of HaNC-RC v.2 can only be realised if GPs have the appropriate training and procedures in place to triage patients to the appropriate specialist clinic. This is echoed by a recent study, interviewing HaN consultants in the UK, which highlighted that the current system of GP referrals for suspected cancers needs to be reviewed due to the number of inappropriate referrals and low detection rates, and stressed the need for education of the primary care sector in the cancer red flags.<sup>23</sup> Risk calculators such as the HaNC-RC v.2 could be used as an aid to identify high-risk patients seen in the primary care sector, and to support decision-making for onward referral to specialist HaN clinics. A similar model has been used successfully in the Netherlands for referrals of patients with possible prostate cancer, having a positive predictive value of 79% and a 100% negative predictive value for clinically significant prostate cancer (Gleason >7).<sup>24</sup>

On the other hand, a recent survey of UK general practices showed that only 36% have access to cancer decision support tools, and only 16% are likely to use them.<sup>25</sup> Possible reasons for the underuse of such resources include the fact that some normograms require investigations that are not available to the primary care sector, and that in some cases, several calculators are available, with little guidance on which one to use. Whilst the last point has been addressed to some degree by the development of the Risk Assessment Tools (RAT) and the QCancer score tools which are endorsed by Cancer Research UK and have been incorporated into the GP software systems since 2013,<sup>10,13,26</sup> they do not yet cover all types of cancer, such as HNC. Given the high predictive power of our revised calculator, and the fact that it is purely symptoms and demographics-based, it could be easily integrated into one of the above tools.

In the meantime, another possibility to improve referral routes would be for trained healthcare professionals to use the HaNC-RC in triage clinics based in the hospital or by telephone interview, with subsequent allocation of patients to USOC or more routine appointment. Finally, whilst improving GP referral to specialist clinics should have a substantial impact on how quickly a suspected cancer patient is diagnosed, health professionals still depend on this person seeking an initial appointment at the appropriate time. More work thus needs to be done to raise public awareness of the early warning signs. Given that our calculator is based on demographics and symptoms that can be easily understood by non-specialists, there is potential to translate it into a tool that patients can use to establish whether they should seek medical advice, similar to that used in prostate cancer risk calculators.

### 4.3 | Limitations of the study and future directions

One of the limitations of this study is that the calculator was designed from data collected from only one region in Scotland which could limit the generalisability of the model. Nevertheless, previous study has shown directly comparable demographics, symptoms presentation and cancer detection outcomes between Scottish and English cohorts, making the calculator relevant for use across the UK.<sup>17</sup> Additionally, the HaNc-RC v2 has only been internally validated. Further work is required on external validation of the HaNC-RC v2, and prospective audits of the possible models are needed to establish the best pathway, detection outcomes and long-term outcomes of patients being triaged using the calculator.

It will be also interesting to investigate whether machine learning techniques can improve further the 88.6% prediction power of the HaNC-RC v2. Nevertheless, our multivariable logistic regression performed better than the best selected machine learning model in the publication by Moore et al, with a sensitivity of 7.7% and a specificity of 25.8% but their selected probability cut-off used was not provided for direct comparisons.<sup>19</sup>

We hope that despite these limitations, we have generated the groundwork for further research in the use of a risk calculator for HNC. Beyond further work on validation, we should also consider pathways for clinical implementation of the tool.

## 5 | CONCLUSIONS

Improvement of the detection rate of cancer in the HaN clinics is possible with the use of a cancer prediction model. The second version of the head and cancer risk calculator has achieved a very high prediction power using a combination of significant symptoms, patients' demographics and social history factors. With this high prediction power, it has not only significant potential to improve patients' outcomes but also contribute to better allocation of NHS resources by redesigning the running of the head and clinics. External

validation of the new version of the tool is required as well as trial of its use as a triaging aid.

## ACKNOWLEDGEMENTS

We would like to thank Mr Hitesh Tailor for his help in the update of the orlhealth.com website.

## CONFLICTS OF INTEREST

None.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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## REFERENCES

- Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EURO CARE-4 study. *Lancet Oncol*. 2007;8(9):773–783. Erratum. In: *Lancet Oncol*. 2007;8(10):868. Bielska-Lasota, Magdalena.
- De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EURO CARE-5—a population-based study. *Lancet Oncol*. 2014;15(1):23–34.
- Neal RD. Do diagnostic delays in cancer matter? *Br J Cancer*. 2009;101(Suppl 2):S9–S12.
- Internal data analysis of Cancer Incidence Statistics for England in 2015. Office for national statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationsstatisticsengland/previousReleases>. Accessed June 3, 2019.
- Northern Ireland Cancer Registry. *Northern Ireland Cancer Registry, Queens University Belfast, Incidence by stage 2010–2014*. Belfast: NICR; 2016.
- Quality Health. Cancer patient experience survey, England. 2016. [www.ncpes.co.uk/index.php/reports/2016-reports](http://www.ncpes.co.uk/index.php/reports/2016-reports). Accessed September 5, 2019.
- National Cancer Institute. The nation's investment in cancer research. A plan and budget proposal for the fiscal year 2006. 2006.
- Thrift AP, Whiteman DC. Can we really predict risk of cancer? *Cancer Epidemiol*. 2013;37(4):349–352.
- Usher-Smith J, Emery J, Hamilton W, Griffin SJ, Walter FM. Risk prediction tools for cancer in primary care. *Br J Cancer*. 2015;113(12):1645–1650.
- Gray EP, Teare MD, Stevens J, Archer R. Risk prediction models for lung cancer: a systematic review. *Clin Lung Cancer*. 2016;17(2):95–106.
- Williams TG, Cubiella J, Griffin SJ, Walter FM, Usher-Smith JA. Risk prediction models for colorectal cancer in people with symptoms: a systematic review. *BMJ Gastroenterol*. 2016;16(1):63.
- Q Cancer. 2012. <https://qcancer.org>. Accessed November 11, 2019.
- National Cancer Registration and Analysis Service (NCRAS). Routes to diagnosis; 2006–2013. 2016.
- NHS England Interim Management and Support. Delivering cancer waiting times: a good practical guide. <https://www.england.nhs.uk/wp-content/uploads/2015/03/delivering-cancer-wait-times.pdf>. Accessed October 9, 2019.
- Langton S, Siau D, Bankhead C. Two-week rule in head and neck cancer 2000–14: a systematic review. *Br J Oral Maxillofac Surg*. 2016;54(2):120–131.
- Tikka T, Pracy P, Paleri V. Refining the head and neck cancer referral guidelines: a two-centre analysis of 4715 referrals. *Clin Otolaryngol*. 2016;41(1):66–75.
- Tikka T, Paleri P, MacKenzie K. External validation of a cancer risk prediction model for suspected head and neck cancer referrals. *Clinical Otolaryngol*. 2018;43(2):714–717.
- Lau K, Wilkinson J, Moorthy R. A web-based prediction score for head and neck cancer referrals. *Clin Otolaryngol*. 2018. [Epub ahead of print].
- Moor JW, Paleri V, Edwards J. Patient classification of two-week wait referrals for suspected head and neck cancer: a machine learning approach. *J Laryngol Otol*. 2019;2:1–4.
- Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Ann Oncol*. 2015;26(5):848–864.
- HaNC-RC V.2. Symptoms Based Risk Calculator for head and Neck Cancer Referrals V.2. 2019. Available at: <http://www.orthelth.com/risk-calculator-2.html>
- Allam A, Nijim H. Persistent Unilateral Sore Throat: Should it be included in the 2-week-wait referral criteria by NICE. *Int J Otolaryngol*. 2019;2019:4920514.
- Langton S, Rijken JA, Bankhead CR, Plüddemann A, Leemans CR. Referrals for head and neck cancer in England and The Netherlands: an international qualitative study of the views of secondary-care surgical specialists. *Br J Oral Maxillofac Surg*. 2019;57(2):116–124.
- Osses DF, Alberts AR, Bausch GCF, Roobol MJ. Multivariable risk-based patient selection for prostate biopsy in a primary health care setting: referral rate and biopsy results from a urology outpatient clinic. *Transl Androl Urol*. 2018;7(1):27–33.
- Price S, Spencer A, Medina-Lara A, Hamilton W. Availability and use of cancer decision-support tools: a cross-sectional survey of UK primary care. *Br J Gen Pract*. 2019;69(684):e437–e443.
- Risk Assessment Tool (RAT). Cancer research UK. [https://www.cancerresearchuk.org/health-professional/diagnosis/suspected-cancer-referral-best-practice/risk-assessment-tool-rat#CDS\\_RAT0](https://www.cancerresearchuk.org/health-professional/diagnosis/suspected-cancer-referral-best-practice/risk-assessment-tool-rat#CDS_RAT0). Accessed November 15, 2019.

**How to cite this article:** Tikka T, Kavanagh K, Lowit A, et al. Head and neck cancer risk calculator (HaNC-RC)—V.2. Adjustments and addition of symptoms and social history factors. *Clin Otolaryngol*. 2020;00:1–9. <https://doi.org/10.1111/coa.13511>