

## ORIGINAL RESEARCH

## Prognostic value of H-index in patients surgically treated for squamous cell carcinoma of the larynx

Paolo Boscolo-Rizzo MD<sup>1</sup> | Enrico Zanelli MD<sup>1</sup> | Fabiola Giudici ScD<sup>2</sup> |  
 Francesca Boscolo-Nata MD<sup>3</sup>  | Giovanni Cristalli MD<sup>3</sup> |  
 Alberto Deganello MD, PhD<sup>4</sup>  | Michele Tomasoni MD<sup>4</sup>  | Cesare Piazza MD<sup>4</sup> |  
 Paolo Bossi MD<sup>5</sup> | Giacomo Spinato MD<sup>6</sup> | Anna Menegaldo MD<sup>6</sup> |  
 Enzo Emanuelli MD<sup>6,7</sup> | Piero Nicolai MD<sup>7</sup> | Luigia Bandolin MD<sup>7</sup> |  
 Andrea Ciorba MD<sup>8</sup> | Stefano Pelucchi MD<sup>8</sup> | Valentina Lupato MD<sup>9</sup> |  
 Vittorio Giacomarra MD<sup>9</sup> | Gabriele Molteni MD<sup>10</sup>  | Daniele Marchioni MD<sup>10</sup> |  
 Pietro Canzi MD<sup>11</sup>  | Simone Mauramati MD<sup>11</sup> | Alfonso Fortunati MD<sup>1</sup> |  
 Margherita Tofanelli MD<sup>1</sup> | Daniele Borsetto MD<sup>12</sup>  | Jonathan Fussey MD<sup>13</sup> |  
 Giancarlo Tirelli MD<sup>1</sup>

<sup>1</sup>Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy

<sup>2</sup>Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

<sup>3</sup>Unit of Otorhinolaryngology, Ospedali Riuniti Padova Sud "Madre Teresa Di Calcutta", Monselice, Italy

<sup>4</sup>Department of Otolaryngology—Head and Neck Surgery, University of Brescia, Brescia, Italy

<sup>5</sup>Medical Oncology Unit, Department of Medical Oncology, ASST Spedali Civili di Brescia, Brescia, Italy

<sup>6</sup>Unit of Otolaryngology, AULSS 2—Marca Trevigiana, Treviso, Italy

<sup>7</sup>Department of Neurosciences, Section of Otolaryngology, University of Padova, Padova, Italy

<sup>8</sup>ENT Department, University Hospital of Ferrara, Ferrara, Italy

<sup>9</sup>Unit of Otolaryngology, Azienda Ospedaliera "S. Maria degli Angeli", Pordenone, Italy

<sup>10</sup>Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Section of Otolaryngology, University of Verona, Verona, Italy

<sup>11</sup>Department of Otolaryngology, University of Pavia, IRCCS Policlinico "San Matteo" Foundation, Pavia, Italy

<sup>12</sup>Department of ENT, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

<sup>13</sup>Department of ENT/Head and Neck Surgery, University Hospital Birmingham, Birmingham, UK

## Correspondence

Daniele Borsetto, Department of ENT,  
 Addenbrooke's Hospital, Cambridge University  
 Hospitals NHS Foundation Trust, Cambridge,  
 UK.

Email: db847@cam.ac.uk

## Abstract

**Objective:** Recently, a novel host-related index, the Host-index (H-index), including both inflammatory and nutritional markers, has been described and observed to stratify prognosis in patients with squamous cell carcinoma (SCC) of the oral cavity more accurately than other host-related indexes. This study aimed to investigate the prognostic performance of the H-index using pretreatment blood tests in patients receiving up-front surgery for SCC of the larynx.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC, on behalf of The Triological Society.

**Methods:** This retrospective observational study included a multicenter series of consecutive patients with SCC of the larynx diagnosed between 1 January 2009 and 31 July 2018, whose pretreatment blood tests were available and included the parameters necessary for the calculation of neutrophil to lymphocyte ratio (NLR) and the H-index. Their association with disease-free survival (DFS) and overall survival (OS) was measured.

**Results:** A total of 231 patients were eligible for the present analysis (median [range] age, 68 [37-96] years; 191 [82.7%] men). The median follow-up was 73 months. In multivariable Cox proportional hazards regression models, increasing age (adjusted hazard ratio [aHR], 1.07 per year; 95% CI, 1.04-1.09), advanced pT stage (aHR = 1.71; 95% CI: 1.07-2.71), and having close or positive surgical margins (aHR = 2.01; 95% CI: 1.21-3.33) were significantly associated with poor OS. Among blood parameters, a higher neutrophil count was a strong predictor of both worse DFS (aHR for recurrence/death = 2.34; 95% CI: 1.24-4.40) and OS (aHR for death = 2.67; 95% CI: 1.51-4.71). Among inflammatory blood indexes, while NLR was not significantly associated with DFS or OS, patients with H-index  $\geq 8.37$  showed a higher aHR for both recurrence/death (2.82; 95% CI: 1.65-4.79) and death (2.22; 95% CI: 1.26-3.89).

**Conclusion:** In conclusion, the present study confirms the prognostic value of pretreatment H-index, an easily measurable inflammatory and nutritional index, in patients with SCC of the larynx.

**Level of Evidence:** III

#### KEYWORDS

H index, inflammation, larynx, prognosis, squamous cell carcinoma

## 1 | INTRODUCTION

Despite evidence that host-related factors can significantly influence outcomes in cancer patients, their use in prognostication is still limited, with the emphasis being on tumor parameters in clinical practice.

As inflammation and immune surveillance play a pivotal role in cancer development, several inflammation parameters and indexes have been investigated as potential markers for prognosis in various types of cancer. In the context of the tumor microenvironment (TME), several pro-inflammatory mediators are produced by both the tumor cells and the stroma. These cytokines recruit inflammatory cells such as neutrophils, monocytes, and myeloid-derived suppressor cells from the bloodstream, enriching the inflammatory TME and enhancing cell proliferation and survival, tumor migration, inhibition of adaptive immunity, and neo-angiogenesis, thus leading to cancer growth and progression.<sup>1</sup> In several cancers including head and neck squamous cell carcinoma (HNSCC), raised peripheral neutrophil and monocyte counts have been associated with a poorer prognosis.<sup>2</sup> Conversely, as they are highly immunogenic, cancer cells can induce efficient anti-tumor immunity with T lymphocytes playing a crucial role in the host immune response to cancer: both a high number of tumor infiltrating<sup>3-5</sup> and blood circulating lymphocytes<sup>2,6</sup> have been observed to be associated with better outcome in HNSCC.

Another host-related factor intensively investigated with respect to its prognostic capability is nutritional status. Several parameters are used as surrogate markers for nutritional status, with albumin levels and body mass index (BMI) being the most investigated in oncology. A number of studies have indicated that hypoalbuminemia is associated with decreased survival of cancer patients, including HNSCC.<sup>7</sup> BMI has a U-shaped relationship with mortality, with both underweight and overweight patients having poorer prognoses than those with a healthy BMI.<sup>8</sup> Also, anemia has been consistently found to be an independent prognostic factor for poor survival in several solid malignant tumors<sup>9</sup> including HNSCC.<sup>8</sup> The development of anemia in cancer is likely to be multifactorial, deriving from complex interactions between the immune system, TME, and cancer cells but also as consequence of malnutrition.<sup>10</sup>

To combine the above-mentioned measures of inflammation into composite markers of systemic inflammatory response, several indexes have been proposed. Among these, the neutrophil to lymphocyte ratio (NLR), being relatively low-cost, readily accessible from a full blood count with differential, and simple to calculate, is the most extensively investigated.<sup>11</sup> This ratio was developed by comparing pro-inflammatory and cancer promoting immune cells, that is, neutrophils, and anti-inflammatory or cancer suppressive cells, that is, lymphocytes.<sup>12</sup> Recently, an umbrella

review of systematic reviews and meta-analyses of observational studies confirmed the strong association between a high NLR and poor prognosis in cancer patients.<sup>11</sup> Interestingly, an inverse correlation was observed between the NLR and the number of tumor-infiltrating CD8+ T cells in the TME, thus supporting the theory that the peripheral blood compartment may contribute to the immune milieu in the TME.<sup>13</sup>

Very recently, a novel and more complete index, the Host-index (H-index), including both inflammatory and nutritional aspects was developed.<sup>14</sup> This index was proposed by Valero et al, and includes two host-factors (neutrophils and monocytes) which are inversely associated with survival as the numerator, with three other variables (hemoglobin, albumin, and lymphocytes) associated with a good outcome as the denominator. The H-index has been shown to stratify prognosis in a large cohort of patients with SCC of the oral cavity more accurately than other host-related indexes.<sup>14</sup>

This study aimed to investigate the prognostic role of H-index using pretreatment blood tests in patients receiving up-front surgery for squamous cell carcinoma (SCC) of the larynx.

## 2 | METHODS

### 2.1 | Inclusion criteria

A multicenter retrospective observational study conducted with the approval of the ethics committee of Treviso/Belluno provinces (Date March 23th 2020/No. 773/CE Marca) was performed in a cohort of consecutive chemotherapy- and radiotherapy-naïve patients, who underwent upfront surgery +/- adjuvant (chemo)radiotherapy for nonmetastatic SCC of the larynx from 1 January 2009 to 31 July 2018. The study network included General and University Hospitals in North Italy, located in Brescia, Ferrara, Monselice, Padova, Pavia, Pordenone, Treviso, Trieste, and Verona. Inclusion criteria were (a) head and neck squamous cell carcinoma (HNSCC) arising from the larynx; (b) curative upfront surgery as primary treatment modality; and (c) availability of preoperative blood parameters necessary for the calculation of the NLR and H-index. Patients were specifically excluded if (a) they were diagnosed with T1 glottic SCC; (b) they had any coexisting conditions or hematological conditions that could alter inflammatory parameters; (c) they had previous malignancy or additional synchronous primary tumors; (d) their pretreatment blood test results were not available; and (e) they had metastatic disease.

### 2.2 | Participants and data

Medical records were reviewed to collect sociodemographic and clinical characteristics of enrolled patients. Baseline characteristics, including gender, age, smoking habits, drinking habits, cancer site, pathological TNM staging (eighth edition), grading, surgical

**TABLE 1** Clinicopathological characteristics of the cohort

Characteristic	Finding (N = 231) <sup>a</sup>
Age, median (range), y	68 (37-96)
Sex	
Male	191 (82.7%)
Female	40 (17.3%)
Smoking habits	
Never	17 (7.3%)
Ever	181 (78.4%)
Missing	33 (14.3%)
Drinking habits	
Never	98 (42.4%)
Current	74 (32.0%)
Missing	59 (25.5%)
Grading	
1	17 (7.4%)
2	120 (52.0%)
3	68 (29.4%)
Missing	26 (11.2%)
pT <sup>b</sup>	
2	81 (35.0%)
3	87 (37.7%)
4	63 (27.3%)
pN <sup>b</sup>	
0	156 (67.5%)
1	14 (6.1%)
2	37 (16.0%)
3	24 (10.4%)
pStage <sup>b</sup>	
II	61 (26.4%)
III	69 (29.9%)
IV	101 (43.7%)
Extracapsular extension	
Absent	201 (87.0%)
Present	30 (13.0%)
Margins	
Negative	187 (80.9%)
Close	23 (10.0%)
Positive	21 (9.1%)
Adjuvant treatment	
Radiotherapy alone	74 (32.0%)
Chemoradiotherapy	36 (15.6%)
No	121 (52.4%)

<sup>a</sup>Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup>According to the eighth Edition TNM Classification for Head and Neck Cancer, American Joint Committee on Cancer, 2017.

margins, and extracapsular extension, were retrieved. A margin was classified as positive if there was invasive cancer present at the inked edge of the specimen or if cancer was less than 1 mm

from the inked edge; close if 1-5 mm; and negative if >5 mm distant from the inked edge. Blood parameters collected at baseline included hemoglobin (g/L), neutrophils ( $10^3/\mu\text{L}$ ), lymphocytes ( $10^3/\mu\text{L}$ ), monocytes ( $10^3/\mu\text{L}$ ), and albumin (g/dL). Patients were routinely followed-up according to consensus guidelines<sup>15</sup> with endoscopic examination of the upper aero-digestive tract every 1-3 months for the first year, 3-4 months during the second year, 4-6 months during the third year, and every 6 months thereafter. A chest CT scan was annually performed in patients with history of smoking  $\geq 20$  packs/year. Additional dedicated head and neck imaging was performed based on clinical features and local protocol.

## 2.3 | Inflammatory indexes

Using pretreatment blood parameters, we calculated the NLR [neutrophils/lymphocytes] and the H-index [(neutrophils  $\times$  monocytes)/[lymphocyte  $\times$  hemoglobin  $\times$  albumin]  $\times$  100).

## 2.4 | Statistical analysis

The primary and secondary outcomes were the overall survival (OS) rate and the disease-free survival (DFS) rate, respectively, according to different H-index values. Descriptive statistics of patient

**TABLE 2** Hazard ratio (HR) of progression and death and corresponding 95% confidence intervals (CI)<sup>a</sup> according to socio-demographic and clinical characteristics

	Patients	Disease-free survival			P-value	Overall survival			P-value
		Events	5 years (%)	HR (95% CI) <sup>a</sup>		Events	5 years (%)	HR (95% CI) <sup>a</sup>	
Gender									
Female	40	14	71.6	1.00 (Reference)		12	78.7	1.00 (Reference)	
Male	191	96	52.3	1.45 (0.81-2.60)	.216	83	57.6	1.41 (0.75-2.63)	.289
Age (years)									
<60	33	7	78.8	1.05 (1.03-1.07) <sup>b</sup>	<.001	2	93.9	1.07 (1.04-1.09) <sup>b</sup>	<.001
60-69	99	43	58.7			36	63.3		
70-79	73	41	49.8			39	53.6		
$\geq 80$	26	19	30.8			18	31.9		
Smoking habits									
Never	17	6	70.6	1.00 (Reference)		6	76.5	1.00 (Reference)	
Ever	181	85	54.5	1.53 (0.65-3.61)	.331	72	60.1	1.21 (0.51-2.87)	.760
Missing	33	19	54.2	1.53 (0.52-4.51)	.444	17	57.6	0.97 (0.32-2.95)	.956
Drinking habits									
Never	98	44	59.7	1.00 (Reference)		36	52.7	1.00 (Reference)	
Ever	74	37	48.0	0.98 (0.62-1.55)	.932	33	67.6	0.95 (0.58-1.57)	.832
Missing	59	29	57.9	0.91 (0.48-1.73)	.773	26	61.0	1.08 (0.54-2.16)	.838
pT									
pT1-T2	81	40	55.2	1.00 (Reference)		32	63.3	1.00 (Reference)	
pT3-T4	150	70	55.9	1.31 (0.87-1.99)	.189	63	60.2	1.71 (1.07-2.71)	.024
pN									
pN0-pN1	170	73	59.8	1.00 (Reference)		60	67.2	1.00 (Reference)	
pN2-pN3	61	37	44.2	1.08 (0.69-1.68)	.741	35	45.5	1.39 (0.87-2.21)	.169
Grading									
G1	17	5	82.4	1.00 (Reference)		4	82.4	1.00 (Reference)	
G2	120	52	58.3	1.47 (0.57-3.80)	.431	41	66.9	1.55 (0.53-4.56)	.422
G3	68	39	40.2	2.04 (0.77-5.40)	.150	37	42.5	2.61 (0.89-7.67)	.081
Missing	26	14	64.9	1.64 (0.58-4.62)	.351	13	69.2	2.10 (0.67-6.17)	.205
Surgical margins									
Negative	187	79	61.2	1.00 (Reference)		70	65.8	1.00 (Reference)	
Close/positive	44	31	32.2	2.32 (1.47-3.67)	<.001	25	42.4	2.01 (1.21-3.33)	.007

<sup>a</sup>Estimated from Cox proportional hazard model, adjusted for gender, age, pT, pN, and surgical margins.

<sup>b</sup>Age considered as continuous variable.

**TABLE 3** Hazard ratio (HR) of progression and death and corresponding 95% confidence intervals (CI)<sup>a</sup> according blood parameters, NLR, and H-index

	Patients	Disease-free survival			P-value	Overall survival			P-value
		Events	5 years (%)	HR (95% CI) <sup>a</sup>		Events	5 years (%)	HR (95% CI) <sup>a</sup>	
Hemoglobin <sup>b</sup>									
Normal values	145	56	66.4%	1.00 (Reference)		47	70.6%	1.00 (Reference)	
Low values	86	54	37.3%	1.80 (1.21-2.68)	.004	48	45.5%	1.74 (1.14-2.68)	.011
Lymphocytes									
>1.18	207	94	58.2%	1.00 (Reference)		82	63.2%	1.00 (Reference)	
≤1.18	24	16	30.0%	1.68 (0.96-2.96)	.071	13	42.1%	1.50 (0.80-2.82)	.205
Monocytes									
≤0.58	102	57	59.7%	1.00 (Reference)		39	66.2%	1.00 (Reference)	
0.59-1.00	101	43	58.3%	1.02 (0.67-1.56)	.918	39	61.8%	1.22 (0.77-1.94)	.392
≥1.01	28	28	33.7%	1.86 (1.08-3.21)	.026	17	42.9%	2.20 (1.21-3.98)	.009
Neutrophils									
≤4.80	119	49	62.5%	1.00 (Reference)		43	65.6%	1.00 (Reference)	
4.81-7.98	87	43	53.0%	1.21 (0.79-1.85)	.389	38	59.4%	1.18 (0.75-1.85)	.483
≥7.99	25	18	32.0%	2.67 (1.51-4.71)	<.001	14	48.0%	2.34 (1.24-4.40)	.008
Albumin									
≥4.61	15	4	80.0%	1.00 (Reference)		3	78.8%	1.00 (Reference)	
3.76-4.60	144	62	59.9%	2.05 (0.74-5.72)	.169	53	64.5%	2.27 (0.70-7.36)	.174
≤3.75	72	44	41.9%	2.88 (1.01-8.20)	.047	39	51.1%	3.12 (0.95-10.23)	.061
NLR									
≤1.35	28	10	63.8%	1.00 (Reference)		8	68.6%	1.00 (Reference)	
1.36-3.85	154	70	57.9%	0.94 (0.48-1.86)	.865	62	62.2%	0.92 (0.43-1.95)	.822
≥3.86	49	30	43.3%	1.51 (0.73-3.13)	.271	25	53.6%	1.20 (0.53-2.71)	.667
H-index									
≤3.60	148	57	65.2%	1.00 (Reference)		49	68.6%	1.00 (Reference)	
3.61-8.36	53	31	41.8%	1.68 (1.07-2.64)	.025	28	50.0%	1.73 (1.07-2.79)	.026
≥8.37	30	22	32.7%	2.82 (1.65-4.79)	<.001	18	46.2%	2.22 (1.26-3.89)	.006

Abbreviations: H-index, host-index; NLR, neutrophil to lymphocyte ratio.

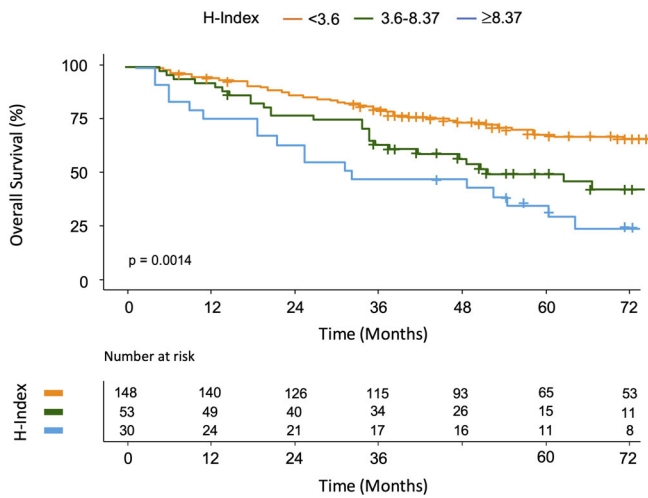
<sup>a</sup>Estimated from Cox proportional hazard model, adjusted for gender, age, pT, pN, and surgical margins.

<sup>b</sup>Low values: Hemoglobin <12 g/dL for female and <14 g/dL for male.

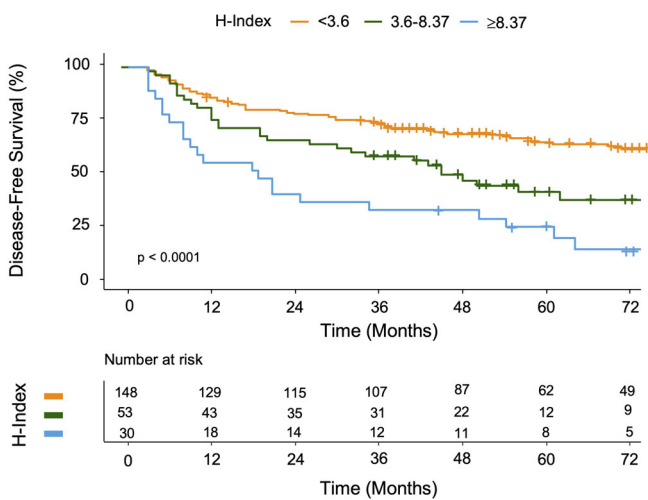
demographics and clinical characteristics were reported as frequencies (proportions) for categorical variables, and median (range max-min) for continuous variables. OS and DFS were used as the endpoint for survival analysis. OS was defined as the length of time from treatment to death from any cause. DFS was defined as the length of time from treatment to the first evidence of clinical recurrence (loco-regional or distant) or death from any cause. Median follow up time was based on the Kaplan-Meier method applied to the censored times reversing the roles of event status and censored. The associations between age, gender, smoking, alcohol, pathological tumor (pT) and regional nodal (pN) stage, and surgical margins, and survival was analyzed using a univariate Cox proportional hazard regression analysis. The resultant significant variables were selected as candidate prognostic indicators. Similarly, we investigated the role of blood parameters (hemoglobin, lymphocytes, monocytes, neutrophils, and albumin), NLR, and H-index performing a multivariate Cox regression models adjusted for age,

gender, pT, pN, and surgical margins. Results were reported with Hazard Ratios (HR) and 95% confidence intervals (95%CI). Hemoglobin level was categorized as low or normal according to gender-specific clinical cut-offs (ie, <12 g/dL, and ≥16 g/dL in women; <14 g/dL, ≥14 g/dL in men). For lymphocytes, monocytes, neutrophils, albumin, and NLR, we used the optimal cut-offs of previous studies determined in similar cohort of HNSCC including laryngeal SCC<sup>2,7</sup>; where data in the above studies were unclear, the corresponding author was contacted by e-mail with a request for clarification.

Since there are no previous studies evaluating the prognostic performance of the H-index in laryngeal cancer, in our implementation, recursive partitioning analysis (package “party” [R 4.0.2]) was used to identify the threshold values of the H-Index, by taking into account the censored DFS outcome. These cut-offs were also used to analyze differences in OS. Furthermore, we evaluated the survival difference of expression level dichotomized at the cut-off points using log-rank



**FIGURE 1** Overall survival curve for the host index (H-index)



**FIGURE 2** Disease-free survival curve for the host index (H-index)

tests and Kaplan-Meier curves. A *P*-value of .05 was considered significant. Statistical analysis was performed using R software 4.0.2 (The R foundation for statistical computing, Vienna, Austria).

### 3 | RESULTS

#### 3.1 | Population

A total of 231 patients were eligible for the present analysis (median [range] age, 68 [37-96] years; 191 [82.7%] men). Demographic and clinical characteristics of the cohort are shown in Table 1. The majority of patients presented with advanced stage laryngeal SCC ( $n = 170$ , 73.6%). Negative surgical margins were achieved in 187 patients (80.9%) and nodal metastasis with extracapsular extension was present in 30 cases (13.0%). Adjuvant (chemo)radiotherapy was administered to 110 patients (47.6%). During a median follow-up of

73 months (interquartile range: 54-92), 95 patients died; cancer was the cause of death in 60 (63.2%) of them. Thirty-six patients experienced local recurrence, while 33 patients had regional recurrence and 36 distant metastases, 11 of them concomitantly with local or regional recurrence. A second primary tumor was diagnosed during follow-up in 26 patients.

Adjusted hazard ratios (aHR) for DFS and OS according to demographic and clinical factors are reported in Table 2. In multivariable Cox proportional hazards regression models, increasing age (aHR, 1.07 per year; 95% CI, 1.04-1.09), advanced pT stage (aHR = 1.71; 95% CI: 1.07-2.71), and having close or positive surgical margins (aHR = 2.01; 95% CI: 1.21-3.33) were significantly associated with poor OS with age and close or positive surgical margins being significantly associated also with poor DFS.

Blood samples were obtained a median inter quartile range (IQR) of 16 (8-28) days before surgery. Table 3 shows the aHR for both DFS and OS according to blood parameters and inflammatory indexes. While a low lymphocyte count showed only a trend toward a worse DFS, low hemoglobin levels and higher monocyte and neutrophil counts were significantly associated with both poor DFS and OS. In particular, a higher neutrophil count was a strong predictor of both worse DFS (aHR for recurrence/death = 2.34; 95% CI: 1.24-4.40) and OS (aHR for death = 2.67; 95% CI: 1.51-4.71). The aHR for both DFS and OS increased with decreasing levels of albumin showing a trend toward a worse OS and reaching statistical significance for DFS.

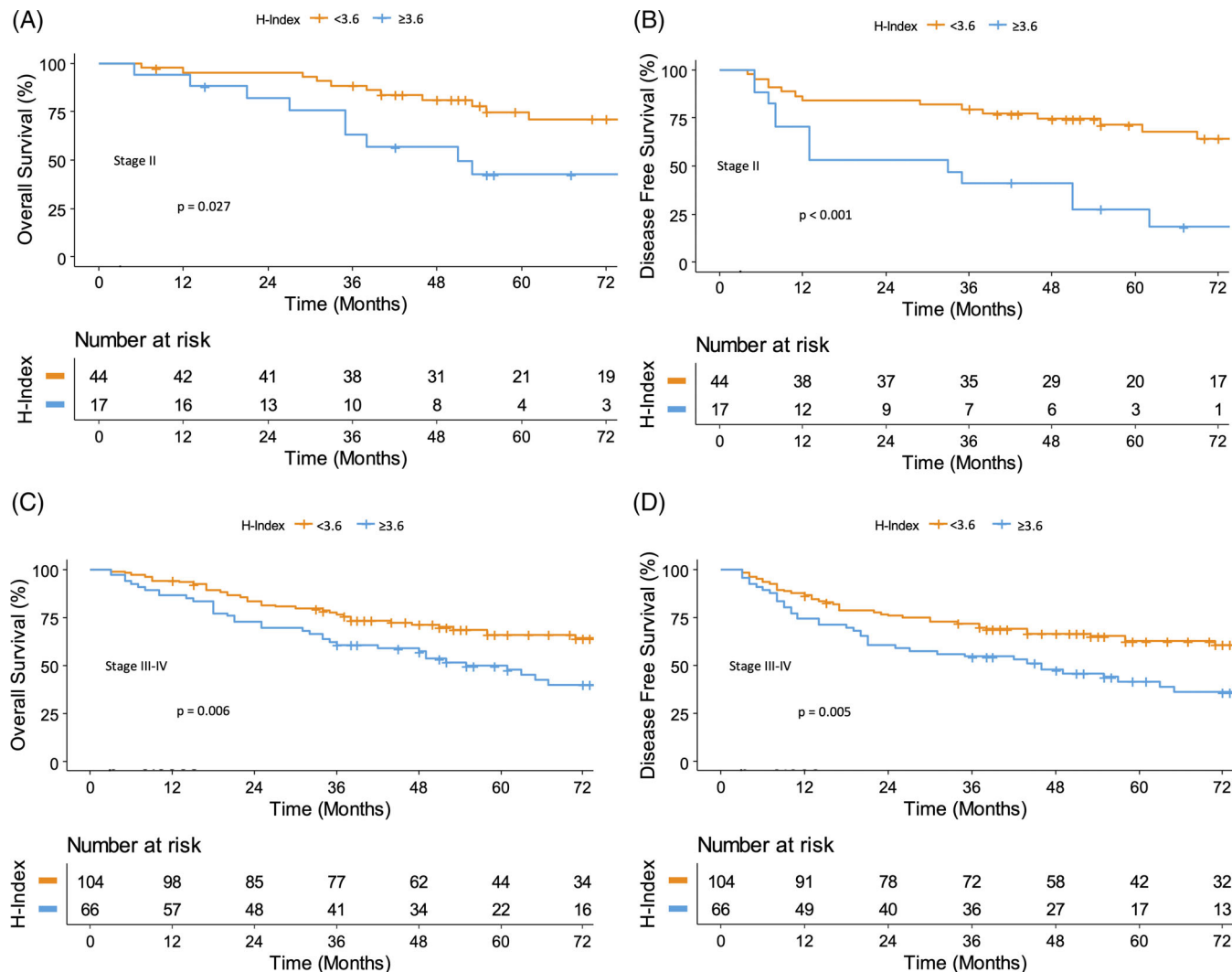
Finally, while NLR was not significantly associated with DFS or with OS, both DFS and OS significantly decreased with increasing H-index category (Table 3). Patients in the higher H-index category showed a higher aHR for both recurrence/death (2.82; 95% CI: 1.65-4.79) and death (2.22; 95% CI: 1.26-3.89). Notably, compared to patients with H-index <3.60, those with H-index  $\geq 8.37$  showed a both worse 5-year OS (46.2% vs 68.6%;  $P = .001$ —Figure 1) and DFS (32.7% vs 65.2%  $P < 0.001$ ; Figure 2). Finally, a significant difference in terms of both OS and DFS according to H-index values was observed both in stage II and stage III-IV patients (Figure 3).

### 4 | DISCUSSION

This study showed that H-index, a novel prognostic host-related cancer index originally investigated in patients with SCC of the oral cavity, is also able to stratify by prognosis in patients surgically treated for SCC of the larynx. Specifically, a high H-index can identify patients at higher risk for both worse DFS (aHR = 2.82) and OS (aHR = 2.22). These results confirm previous findings by Valero et al who first developed this novel index observing its significant prognostic capability in a large cohort of patients with SCC of the oral cavity.<sup>14</sup> Moreover, H-index was observed to significantly stratified the prognosis also in the conventional low risk group of stage II patients.

In keeping with the biological role of neutrophils and monocytes in cancer, both a high count of neutrophils and monocytes were associated with worse DFS and OS, thus confirming the observations in previous studies conducted in cancer patients including those with





**FIGURE 3** A, Overall survival curve for the host index (H-index) in stage II patients; B, disease-free survival curve for the Host Index (H-index) in stage II patients. C, Overall survival curve for the host index (H-index) in stage III-IV patients; D, disease-free survival curve for the host index (H-index) in stage III-IV patients. Due to the low number of patients having an H-index  $\geq 8.37$ , H-index was dichotomized

HNSCC.<sup>2</sup> Monocyte-derived tumor-associated macrophages are indeed drivers of tumor progression by promoting cancer cell proliferation and survival, angiogenesis and lympho-angiogenesis.<sup>16</sup> Similarly, by secreting cytokines and chemokines and releasing reactive oxygen species, neutrophils play an essential role in cancer progression, including promoting angiogenesis, immunosuppression, and cancer metastasis.<sup>17</sup>

In contrast with other reports,<sup>2</sup> although patients with a low lymphocyte count were more likely to suffer recurrence and death, this association did not reach a statistical significance in our study. This may be due to the small number of patients in the high-risk category according to the previously reported cut-offs.<sup>2</sup> Furthermore, unlike other types of leukocytes, lymphocytes are a heterogeneous population of cells that serve diverse functions related to tumorigenesis and cancer progression. While most CD4+ T cells, CD8+ T cells, and natural killer cells have anti-tumoral effects, a subset of CD4+ T cells known as regulatory T cells (Treg) and characterized by the

expression of the master transcription factor forkhead box protein p3, suppress anticancer immunity.<sup>18</sup> Interestingly, it has been observed that the prevalence of Treg in the peripheral blood of gastrointestinal cancer patients is significantly higher than that in healthy volunteers<sup>19</sup> and that the proliferation potential of circulating lymphocyte CD8+ T cells was significantly suppressed compared with healthy controls in patients with lung cancer.<sup>20</sup> Thus, a better characterization of different subtypes of circulating lymphocytes may provide more accurate prognostic information. As a consequence, unlike other studies reporting an association between a high NLR and poor outcome in HNSCC<sup>2</sup> and laryngeal cancer,<sup>21</sup> this ratio was not associated with outcome in the present series. However, other authors have failed to identify an association between preoperative NLR and DFS both in laryngeal<sup>22</sup> and oropharyngeal SCC.<sup>23</sup> Interestingly, in a series of patients with HNSCC, it was observed that the prognostic capability of NLR mostly depended on the number of neutrophils with the lymphocytes contributing limitedly.<sup>2</sup> In this regard, it should also be

considered that use of steroids is more frequent in laryngeal cancer, to reduce oedema and improve breathing, and possibly associated with a transient increase in neutrophil count. Unfortunately, in the current retrospective study, we were not able to consider the impact of this therapy on neutrophil count.

Lower serum albumin levels were observed to be associated with worse DFS in the present series, thus confirming previous findings<sup>7</sup> and highlighting the importance of preoperative nutritional status and the potential value of nutrient supplementation.<sup>24</sup> Indeed, early nutritional intervention in patients with HNSCC results in a better treatment tolerance and an improved outcome.<sup>25</sup> Along with weight loss, anemia is one of the diagnostic criteria for tumor cachexia.<sup>26</sup> Anemia is known to negatively impact the efficacy of (chemo) radiation in patients with HNSCC.<sup>27,28</sup> Anemia (hemoglobin <12 g/dL for women and <14 g/dL for men) was significantly associated with both OS and DFS reduction in the present surgical series. This is consistent with a previous investigation conducted in a large series of patients with SCC of the larynx showing that, independently from comorbidities, anemia has a negative influence on overall survival.<sup>8</sup>

By incorporating different inflammatory parameters and including surrogates of nutritional status, that is, albumin and hemoglobin, the H-Index provides a more comprehensive host-related marker for risk stratification. Based on routinely collected blood parameters not requiring any additional expenditure, this index makes it possible to counterbalance the weight given by the different parameters potentially capable of influencing the prognosis in opposite directions.

The main limitations of this study are the retrospective design and the small sample size. Furthermore, possible noncancer-related conditions affecting the variables needed for H-index calculation could not be accounted for in our study.

In conclusion, although our results need to be interpreted with caution and should be validated in a larger sample, the present study supports the prognostic value of pretreatment H-index, an easily measurable inflammatory and nutritional index, in patients with SCC of the larynx. As the prognostic stratification capability of H-index was independent from conventional variables, this index may help to better identify patients at risk for poor outcome. This is of paramount importance in patient prognostication and counseling.

## CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest.

## AUTHOR CONTRIBUTIONS

Dr Boscolo-Rizzo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Drs Boscolo-Rizzo, Tirelli. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* Drs Boscolo-Rizzo, Zanelli, Giudici, Borsetto, Fussey, Tirelli. *Critical revision of the manuscript for important intellectual content:* Drs Boscolo-Rizzo, Deganello, Bossi, Borsetto, Fussey, Tirelli. *Statistical analysis:* Dr Giudici. *Supervision:* Drs Boscolo-Rizzo and Tirelli. *Final approval of the manuscript:* All authors.

## ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Treviso and Belluno provinces (Date March 23th 2020/No. 773/CE Marca).

## ORCID

Francesca Boscolo-Nata  <https://orcid.org/0000-0003-0758-2376>

Alberto Deganello  <https://orcid.org/0000-0003-1008-7333>

Michele Tomasoni  <https://orcid.org/0000-0003-1298-1654>

Gabriele Molteni  <https://orcid.org/0000-0001-7764-2122>

Pietro Canzi  <https://orcid.org/0000-0002-6471-5035>

Daniele Borsetto  <https://orcid.org/0000-0003-3464-2688>

## REFERENCES

- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454:436-444.
- Valero C, Pardo L, López M, et al. Pretreatment count of peripheral neutrophils, monocytes, and lymphocytes as independent prognostic factor in patients with head and neck cancer. *Head Neck*. 2017;39:219-226.
- Pretscher D, Distel LV, Grabenbauer GG, Wittlinger M, Buettner M, Niedobitek G. Distribution of immune cells in head and neck cancer: CD8+ T-cells and CD20+ B-cells in metastatic lymph nodes are associated with favourable outcome in patients with oro- and hypopharyngeal carcinoma. *BMC Cancer*. 2009;9:292.
- Nguyen N, Bellile E, Thomas D, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. *Head Neck*. 2016;38:1074-1084.
- Borsetto D, Tomasoni M, Payne K, et al. Prognostic significance of CD4+ and CD8+ tumor-infiltrating lymphocytes in head and neck squamous cell carcinoma: a meta-analysis. *Cancer*. 2021;13:781.
- He J-R, Shen G-P, Ren Z-F, et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. *Head Neck*. 2012;34:1769-1776.
- León X, Pardo L, Sansa A, et al. Prognostic significance of albumin levels prior to treatment in patients with head and neck squamous cell carcinoma. *Acta Otorrinolaringol Esp*. 2020;71:204-211.
- te Riele RJLM, Dronkers EAC, Wieringa MH, et al. Influence of anemia and BMI on prognosis of laryngeal squamous cell carcinoma: development of an updated prognostic model. *Oral Oncol*. 2018;78:25-30.
- Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer. *Cancer*. 2001;91:2214-2221.
- Birgegård G, Aapro MS, Bokemeyer C, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. *Oncology*. 2005;68(Suppl 1):3-11.
- Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. *BMC Med*. 2020;18:360.
- Guthrie GJK, Charles KA, Roxburgh CSD, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88:218-230.
- Tanaka R, Kimura K, Eguchi S, et al. Preoperative neutrophil-to-lymphocyte ratio predicts tumor-infiltrating CD8+ T cells in biliary tract cancer. *Anticancer Res*. 2020;40:2881-2887.
- Valero C, Zanoni DK, Pillai A, et al. Host factors independently associated with prognosis in patients with Oral cavity cancer. *JAMA Otolaryngol-Head Neck Surg*. 2020;146:699-707.
- Simo R, Homer J, Clarke P, et al. Follow-up after treatment for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130:S208-S211.



16. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity*. 2014;41:49-61.
17. Wu L, Saxena S, Singh RK. Neutrophils in the tumor microenvironment. *Adv Exp Med Biol*. 2020;1224:1-20.
18. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression – implications for anticancer therapy. *Nat Rev Clin Oncol*. 2019;16:356-371.
19. Tokuno K, Hazama S, Yoshino S, Yoshida S, Oka M. Increased prevalence of regulatory T-cells in the peripheral blood of patients with gastrointestinal cancer. *Anticancer Res*. 2009;29:1527-1532.
20. An N, Wang H, Jia W, et al. The prognostic role of circulating CD8+ T cell proliferation in patients with untreated extensive stage small cell lung cancer. *J Transl Med*. 2019;17:402.
21. Chen L, Zeng H, Yang J, et al. Survival and prognostic analysis of preoperative inflammatory markers in patients undergoing surgical resection for laryngeal squamous cell carcinoma. *BMC Cancer*. 2018;18:816.
22. Wong BYW, Stafford ND, Green VL, Greenman J. Prognostic value of the neutrophil-to-lymphocyte ratio in patients with laryngeal squamous cell carcinoma. *Head Neck*. 2016;38:E1903-E1908.
23. Fanetti G, Alterio D, Marvaso G, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in HPV status era for oropharyngeal cancer. *Oral Dis*. 2020;26:1384-1392.
24. Müller-Richter U, Betz C, Hartmann S, Brands RC. Nutrition management for head and neck cancer patients improves clinical outcome and survival. *Nutr Res N Y N*. 2017;48:1-8.
25. Paccagnella A, Morello M, Da Mosto MC, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Support Care Cancer*. 2010;18:837-845.
26. Couch ME, Dittus K, Toth MJ, et al. Cancer cachexia update in head and neck cancer: definitions and diagnostic features. *Head Neck*. 2015;37:594-604.
27. Boscolo-Rizzo P, Gava A, Marchiori C, Baggio V, Da Mosto MC. Functional organ preservation in patients with locoregionally advanced head and neck squamous cell carcinoma treated by platinum-based multidrug induction chemotherapy and concurrent chemoradiotherapy. *Ann Oncol*. 2011;22:1894-1901.
28. Borsetto D, Polesel J, Tirelli G, et al. Pretreatment high MCV as adverse prognostic marker in nonanemic patients with head and neck cancer. *Laryngoscope*. 2021;131:E836-E845.

**How to cite this article:** Boscolo-Rizzo P, Zanelli E, Giudici F, et al. Prognostic value of H-index in patients surgically treated for squamous cell carcinoma of the larynx. *Laryngoscope Investigative Otolaryngology*. 2021;6(4):729-737. <https://doi.org/10.1002/lio2.603>