Influence of anemia and BMI on prognosis of laryngeal squamous cell carcinoma: development of an updated prognostic model

Roderick te Riele*, Emilie Dronkers*, Marjan Wieringa, Martine De Herdt, Aniel Sewnaik, Jose Hardillo, Robert Baatenburg de Jong.

** Both authors contributed equally to this work.*

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ABSTRACT

The objective of this study was to study the impact of anemia and body mass index (BMI) on survival, and development of a prognostic model for overall survival for patients with laryngeal squamous cell carcinoma (LSCC). A retrospective cohort study was performed including all consecutive patients with LSCC diagnosed and treated at the Erasmus Medical Center between January 2006 and December 2013. Patient- and tumor-specific data were collected using data from the Netherlands Comprehensive Cancer Organization and supplemented with data from patient records available in the Erasmus MC. All comorbidities were scored at the time of diagnosis. In total 788 patients were included. Mean follow-up time was 50 months (SD: ± 30), during which 298 patients (37.8%) died. In both univariate and multivariate analysis BMI and anemia were significant predictors for overall survival. Multivariate analysis was performed using known predictors such as age, TNM-stage and comorbidity (ACE-27). The hazard ratio of anemia was 1.41 (95% CI: 1.05 - 1.90) and of BMI was 0.97 (95% CI: 0.94 - 0.99). BMI had an inverse association with overall survival in both univariate and multivariate survival analysis. Updating and validating an existing prognostic model with addition of anemia and BMI enhanced the performance of the prognostic model (C-statistic) from 0.77 (95% CI: 0.74 – 0.79) to 0.79 (95% CI: 0.77 - 0.82). Anemia and BMI are predictors of overall survival for LSCC, independent of other known predictors of overall survival. Adding anemia and BMI to an existing prognostic model provides better prediction of overall survival.

INTRODUCTION

Malignancies of the head and neck are predominantly located in the oral cavity (including the lips), pharynx (including nasopharynx) and the larynx. The worldwide incidence of these tumors was over 680,000 cases in 2012, resulting in 4.9% of all malignancies. Mortality of head and neck tumors made up 4.6% of all mortality due to a malignant disease.[1]

In the Netherlands, over 38% of all head and neck squamous cell carcinoma (HNSCC) originates from the larynx.[2] Also, laryngeal squamous cell carcinoma (LSCC) has a favorable prognosis compared to HNSCC as a whole.[2] Treatment of LSCC can impair speech, swallowing and breathing, which have a profound impact on the quality of life.[3,4] Prognosis and morbidity of LSCC are therefore significant topics in communication between physicians and their patients.

In the recent past, our research group developed prognostic models to estimate patients' individual prognosis to support decision making.[5,6] In these models, besides cTNM stage and age, comorbidity, scored with the Adult Comorbidity Evaluation 27 (ACE-27), turned out to be an important prognostic factor for overall survival.[7,8]

However, more recent studies show that the presence of anemia and low Body Mass Index (BMI) also negatively impact patient survival of HNSCC. [9,10] A systematic review on the impact of BMI on survival shows better survival for patients with a BMI above 25.0.[10] However, other comorbidities (as measured by ACE-27) or weight loss were not addressed in this study. In addition, the presence of anemia is known to negatively impact the efficacy of radiotherapy [11], but the effect of anemia on overall survival of patients with HNSCC treated otherwise is presently not known. Furthermore, anemia is not taken into account in comorbidity indexes nor in existing prognostic models.

As prognosis is an important factor during patient counseling, insight in the influence of anemia and BMI amongst other comorbidities on survival of head and neck malignancies is needed. Therefore, the purpose of this study is to report on the impact of anemia and BMI on overall survival of LSCC, independent of other comorbidities. The secondary objective is to determine whether adding anemia and BMI improves the existing prognostic model.

METHODS

This study was approved by the ethics committee of the Erasmus Medical Center (Erasmus MC) (MEC number: MEC-2016-751). Patients with glottic and supraglottic squamous cell carcinoma who were diagnosed and treated at the Erasmus MC between January 1st, 2006 and December 31st , 2013, were included in this retrospective study. Patients were excluded in case of a synchronous primary tumor in the head and neck region, when a patient died before completion of diagnostics or when records were incomplete.

Primary outcome of this study was overall survival and the secondary outcome was Harrell's concordance statistic for internal validation of an updated prognostic model.

Data collection

Tumor- and patient-specific data regarding these patients were obtained from the Netherlands Comprehensive Cancer Organization (NCCO) and merged with corresponding data from the patient records of Erasmus MC. Subsequently, the data were manually checked for each patient using available data from the patient records. Incorrect or missing data was either revised or supplemented by the research staff.

If there was any doubt on the validity of the data collected, the patient was discussed by the research staff until a consensus was reached. A log was kept in which the inclusion of patients was recorded.

Definitions

Information on patient specific comorbidities, anemia, intoxications, length, weight and weight loss was scored Both patient- and disease specific data was scored at the time of diagnosis. Comorbidity was scored using the Adult Comorbidity Evaluation-27 (ACE-27). This ACE-27 index consists of 27 different endpoints in 9 organ systems. Severity of comorbidity was classified into four categories: none, slight, moderate and severe (ACE-27 score 0, 1, 2, and 3 respectively). [6,11]

Anemia was defined as hemoglobin levels below 8.5 mmol/L for men and below 7.5 mmol/L for woman, which corresponds to 13.7 and 12.1 g/dL respectively. Length and weight was used to calculate the Body Mass Index (BMI). Patients were categorized in underweight (BMI < 18.5), normal weight (BMI ≥18.5 and <25), overweight (BMI ≥25 and <30), obese (BMI ≥30 and <38) and morbid obese (BMI ≥38). A BMI ≥38 was chosen as the cut-off for morbid obesity (instead of BMI ≥35) as this corresponds to a moderate comorbidity in the ACE-27 comorbidity index.

Weight loss was defined as the percentage of weight patients lost within 6 months prior to diagnosis of the tumor. It was subdivided in no- to mild weight loss (0-5%), moderate weight loss (5 – 10%) and severe weight loss (>10%).

Intoxications were defined as tobacco- and alcohol use. Data on (former) use at the time of diagnosis was collected. If tobacco use had occurred in any time in the past, the total pack years was registered. Marital status was defined as having a partner (either married or having a durable long term relationship), or being either single or widowed. Finally, we recorded if the received therapy was in accordance with standard treatment protocol at the time of diagnosis.

Data on patient follow-up was obtained using the Dutch Civil Registry and data available in the Erasmus MC. Final day of follow-up time for a patient was defined as the final date that the patient was confirmed to be alive. Follow-up ended on the 31st of December 2015, resulting in a minimum follow-up duration of 2 years.

Statistical analysis

The data was analyzed using IBM SPSS (version 21.0) and R (version 3.4.0) statistical software. Descriptive statistics were performed for all variables and, if applicable, the assumption of a Gaussian distribution was verified. Associations between the collected covariates were studied using the Pearson Chi-square test for categorical data and Student t-test or Wilcoxon rank test for continuous data. During univariate analysis, BMI was analyzed as both a continuous and categorical variable. Univariate analysis of overall survival was performed on all available variables by applying Kaplan-Meier analysis (log-rank test) and the Cox proportional hazard regression model was used to calculate the univariate hazard ratios.

Some data were missing for the variables anemia, BMI, weight loss and variables related to intoxications, see Table 1. After analyzing patterns of our missing data, data were considered missing at random (MAR).[12] Since the MAR assumption was plausible, we found multiple imputation (MI) to be the best way to handle our missing data. After analyzing patterns of the missing data, data were considered missing at random. We performed MI using the Markov Chain Monte Carlo (MCMC) function in SPSS and used 5 iterations to account for possible simulation errors. Therefore the missing data were imputed using multiple imputation with the iterative Markov Chain Monte Carlo (MCMC) method. A total of five iterations were performed. Multivariate statistical analysis was performed by using the pooled data of all five iterations in a Cox proportional hazard regression model. Multiplicative interaction terms were taken into account. Covariate selection was performed using all available variables and subsequently eliminating variables using backward

stepwise elimination until all variables left had a p-value below 0.10. Continuous variables used were age at time of diagnosis, pack years and BMI. All other variables used were categorical. For both univariate and multivariate analysis, a p-value lower than 0.05 was considered significant.

After performing multivariate Cox proportional hazard regression analysis of overall survival, we created a prognostic model using all variables previously defined as prognosticators by our study group (Datema et al. in 2010 and Van der Schroeff in 2012).[5,6] The following variables were included for the prior model: gender, tumor site, age at time of diagnosis, TNM-stage and ACE-27 comorbidity score. The prior model was then updated with freshly defined significant prognosticators from our current study. Afterwards, Harrell's concordance statistic (C-statistic) was used to internally validate the model. After creation of the two prognostic models, C-statistic was used to assess the discriminative ability of the model. Internal validation by bootstrapping our data 1000 times corrected for optimism. After internal validation, the C-statistic was used to compare the new model with the prior model. For estimating the C-statistic of this prior model the data of the current study was used.

RESULTS

A total of 819 patients with primary LSCC between January 2006 and December 2013 were identified. Ten patients were excluded for having synchronous primary head and neck tumors. Another sixteen patients were excluded due to the origin of index tumor being subglottic or unspecified. Finally, three patients died before the diagnostic process was completed and two patients were lost to follow-up while it was unknown whether they received therapy. The remaining 788 patients were included in this study. Patient demographics are presented in Table 1.

Mean duration of follow-up was 50 months (SD: ± 30 months), during which 298 patients (37.8%) died. Two-year survival was 79.4% (SD: ± 2,7%) and five year survival was 63.7% (SD: ± 3.5%).

Overall survival

After univariate analysis, the following variables showed a significant correlation with overall survival: age, tumor localization, clinical TNM-staging, received treatment (yes/no), treatment according to standard treatment protocol (yes/no), ACE-27 score, marital status, BMI, weight loss, anemia and pack years. Of these variables, the following variables have hazard rates which increase by year or unit increase: age, pack years and BMI. See Table 2 for an overview of the univariate survival analysis.

Table 1. Demographics of the total patient population (n = 788)

Variables		No. of patients (%)	Missing (%)
Gender	Men	651 (82.6)	-
	Woman	137 (17.4)	
Mean age at time of diagnosis (years)		66 ± 10	-
Tumor localization	Glottis	530 (67.3)	-
	Supraglottis	258 (32.7)	
T – stage	1	19 (2.4)	-
	1A	260 (33.0)	
	1B	52 (6.6)	
	2	183 (23.2)	
	3	192 (24.4)	
	4A	82 (10.4)	
N – stage	0	661 (83.9)	-
	1	55 (7.0)	
	2	68 (8.6)	
	3	4 (0.5)	
M - stage	0	786 (99.7)	-
	1	2 (0.3)	
Treatment given	Yes	765 (97.1)	-
	No	23 (2.9)	
Treated according to protocol	Yes	698 (88.6)	-
	No	90 (11.4)	
Smoking	Current	477 (60.5)	5 (0.6)
	Former	266 (33.8)	
	Non-smoker	40 (5.1)	
Mean pack years		41 ± 22	183 (23.2)
Alcohol	Current	545 (69.2)	6 (0.8)
	Former	178 (22.6)	
	Non-drinker	59 (7.5)	
ACE-27 total score	0 (none)	224 (28,4)	-
	1 (mild)	273 (34.6)	
	2 (moderate)	204 (25.9)	
	3 (severe)	87 (11.0)	
Marital status	With partner	542 (68.8)	35 (4.4)
	No partner	211 (26.8)	
Body Mass Index	< 18.5	28 (3.6)	65 (8.1)
	≥ 18.5 and < 25	294 (37.3)	
	≥ 25 and < 30	275(34.9)	
	≥ 30 and < 38	106 (13.5)	
	≥ 38	21 (2.7)	
Weight loss	< 5%	526 (66.8)	158 (20.0)
	≥ 5% and < 10%	56 (7.1)	
	≥ 10%	48 (6.1)	
Anemia	Yes	121 (15.4)	55 (7.0)
	No	612 (77.7)	

Table 2. Univariate analysis of overall survival of patients with LSCC

Variables		Hazard Ratio (95% CI)	Overall P-value
Gender	Men*	-	0.462
	Women	0.89 (0.65 - 1.22)	
Age at time of diagnosis (years)**		1.05 (1.04 - 1.06)	0.000
Tumor localization	Glottis*	-	0.000
	Supraglottis	2.49 (1.98 - 3.13)	
T-stage	1A + 1*	-	0.000
	1B	1.82 (1.06 - 3.13)	
	2	1.98 (1.39 - 2.82)	
	3	3.84 (2.78 - 5.30)	
	4A	4.47 (3.04 - 6.57)	
N-stage	0*	-	0.000
	1	2.76 (1.94 - 3.94)	
	≥2	2.64 (1.92 - 3.64)	
Treatment given	Yes*	-	0.000
	No	46.40 (27.78 - 77.48)	
Treatment according	Yes*	-	0.000
to protocol	No	3.38 (2.55 - 4.48)	
Smoking	Never*	-	0.965
	Yes	0.98 (0.58 - 1.66)	
	Former	1.02 (0.59 - 1.75)	
Pack years**		1.01 (1.01-1.02)	0.000
Alcohol	Never*	-	0.113
	Yes	0.95 (0.72 - 1.25)	
	Former	1.44 (0.92 - 2.24)	
ACE-27 score	0 (none)*	-	0.000
	1 (mild)	1.86 (1.33 - 2.61)	
	2 (moderate)	2.21 (1.55 - 3.13)	
	3 (severe)	5.95 (4.09 - 8.66)	
Marital status	With partner	-	
	No partner	1.32 (1.03 – 1.69)	0.030
Body Mass Index**		0.96 (0.94 - 0.99)	0.004
Weight loss	<5%*	-	0.000
	≥ 5% and < 10%	2.47 (1.70 - 3.57)	
	≥ 10%	2.53 (1.68 - 3.81)	
Anemia	No*	-	0.000
	Yes	2.81 (2.16 - 3.67)	

*: reference value, **: hazard ratio per unit or year increase.

An increase in BMI was related to a decrease in mortality (Figure 1A). In contrast to the inverse relationship between high BMI and mortality, a J-shaped relationship between BMI and comorbidity could be seen (Figure 2). Both underweight patients and overweight/obese patients showed an increase in moderate to severe comorbidity. Nearly 76.8% of patients who lost more than 5% of their weight in the six months prior to diagnosis had a BMI below 25.0.

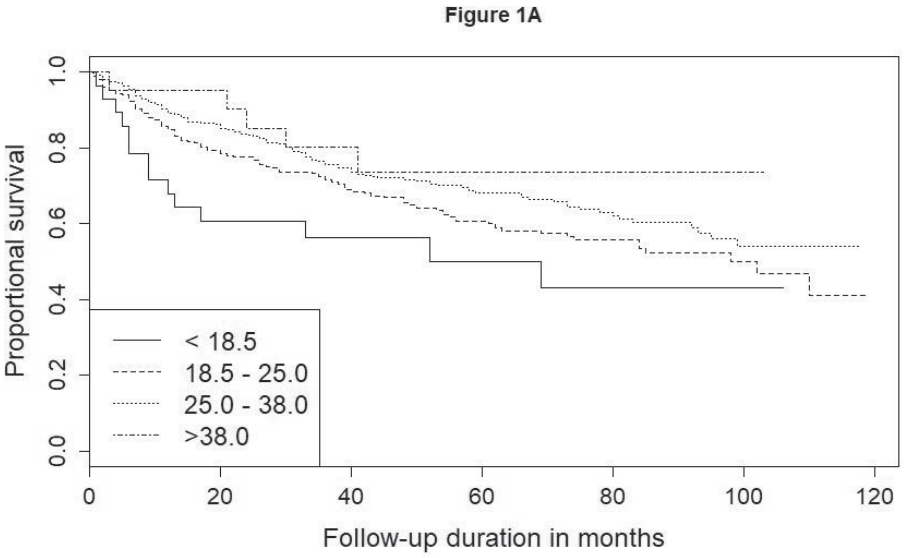
The presence of weight loss showed to be a significant predictor for worse overall survival, with the prognosis of moderate and severe weight loss being similar (Figure 1B). Furthermore, patients with over 5% weight loss had significantly higher T-stage and N-stage (p=0.000). No significant correlation between weight loss and comorbidity could be found.

Presence of anemia showed to have a negative impact on overall mortality (Figure 1C). Anemia was found in 11.3% of all patients with T1-2 LSCC, which is lower when compared to T3 and T4 tumors (23.0 and 32.1% respectively, p=0.000). Additionally, patients with loco-regional lymph node metastasis more often suffered from anemia compared to patients without nodal metastasis (14.8% vs 25.0%, p=0.020). Anemia occurred in 29.6% of patients with moderate to severe weight loss and in 13.1% of patients without weight loss (p=0.000). Finally, anemia had a higher prevalence in patients with severe comorbidity, when compared to patients with no- to moderate comorbidity scores (35.3% versus 14.0%, p=0.000). For an overview of the effect of comorbidity on survival, see Figure 1D.

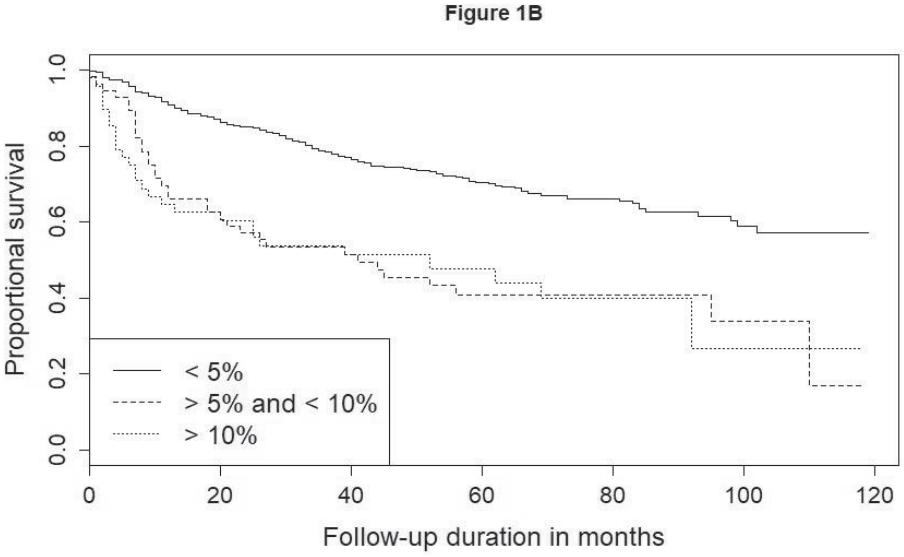
Of all patients, only 90 did not receive treatment according to standard treatment protocols. Of these, 38 patients (38.9%) refused treatment according to guidelines, while the remaining patients (n=52; 61.2%) did not receive therapy according to protocol on the basis of expert opinion. Of the underweight patients, significantly more patients (28.6%) were not treated according to guidelines compared to normal weight (12.2%) or overweight (8.7%) patients (p=0.000). Also anemia was significantly associated with not receiving treatment according to protocol (75.2%) versus 91.2% of all patients without anemia (p=0.000). Similarly, in patients with no- to moderate comorbidity only 9.7% did not receive treatment according to protocol, compared to 26.3% in patients with severe comorbidity (p=0.000).

After establishing the univariate relationship between the tumor- and patient-specific variables mentioned above, multivariate Cox regression survival analysis was performed. A multiplicative interaction term was found between tumor localization and T-stage. All variables except M-stage, pack years, weight loss and 'treatment according to protocol' remained significant after correcting for each variable in the multivariate analysis. An overview of the multivariate analysis is given in Table 3.

Figure 1. Kaplan Meier survival curves for overall survival

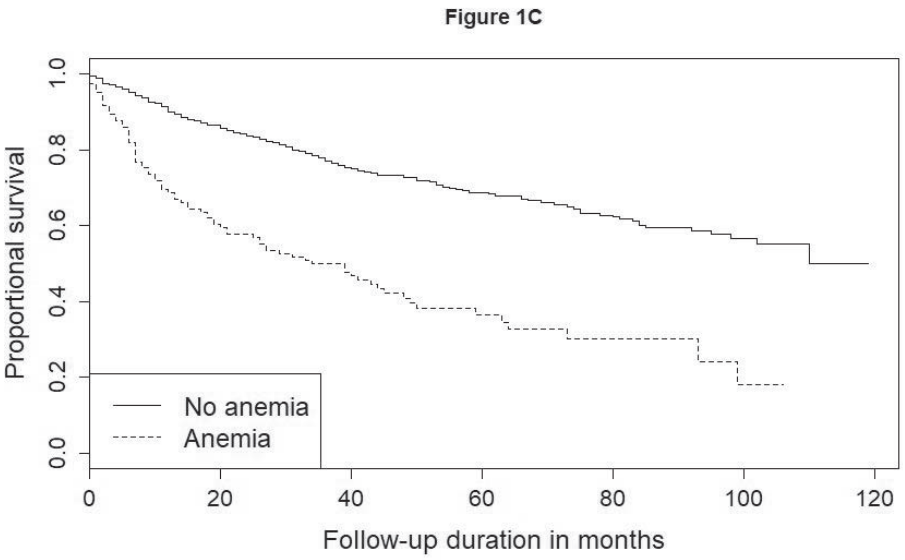


1A. Body Mass Index (categorical),

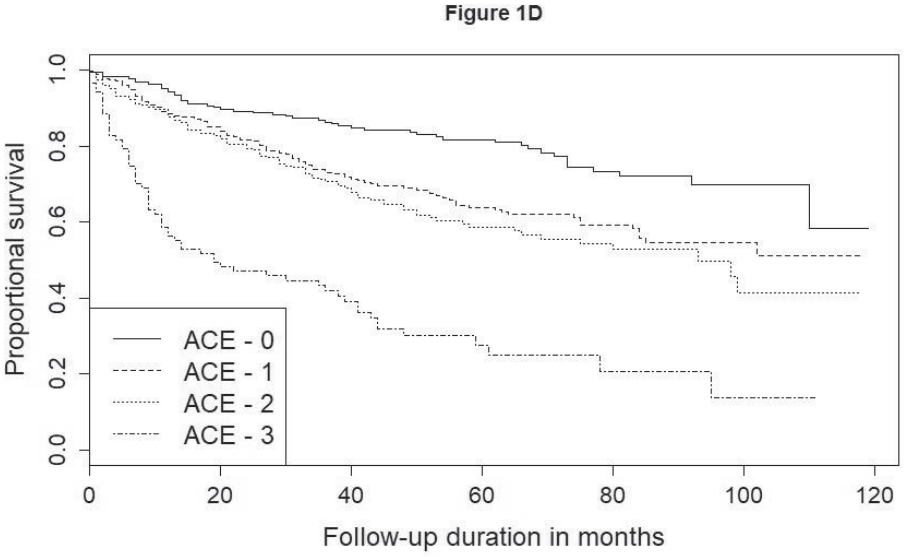


1B: weight loss (in %),

Figure 1. Kaplan Meier survival curves for overall survival

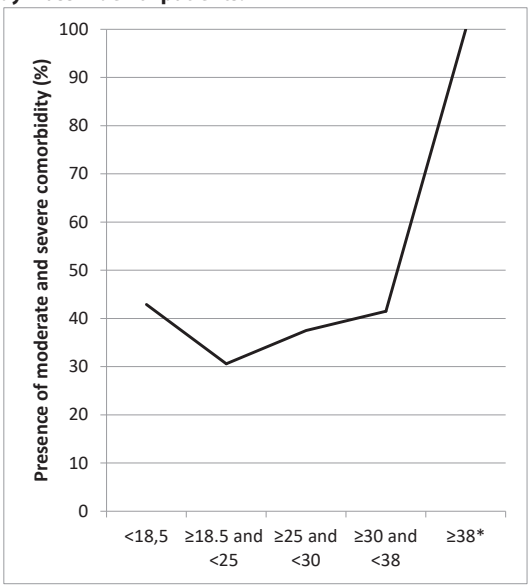


1C: presence of anemia,



1D: comorbidity scored according to the ACE-27 comorbidity index.

Figure 2. Presence of moderate and severe comorbidity scored using the Adult Comorbidity Index – 27, set against the Body Mass Index of patients.



*: in the ACE-27 comorbidity index, a BMI ≥38 is scored as a moderate comorbidity. Therefore all patients had a total comorbidity score of moderate or severe.

Prognostic model comparison

First, we performed a multivariate Cox proportional hazard regression analysis with our LSCC data, using the variables presented in the model as proposed by Datema et al. and Van der Schroeff et al. (gender, 'age at time of diagnosis', tumor localization, cTNM-stage and ACE-27 comorbidity score). [5,6] We bootstrapped our data 1000 times to internally validate this model, We performed internal validation by bootstrapping our data, which resulted in a C-statistic of 0.77 (95% CI: 0.74 – 0.79).

Then, we fitted our new multivariate model, including: gender, 'age at time of diagnosis', tumor localization, cT- and N-stage, ACE-27 comorbidity score, treatment given (yes/no), pack years (continuous), BMI (continuous), weight loss and anemia. Again, we performed internal validation by bootstrapping our data 1000 times, leading to a C-statistic of 0.79 (95% CI: 0.77 – 0.82). The difference between these C-statistics (0.77 and 0.79) was borderline significant.

Table 3. Multivariate analysis of overall survival of patients with LSCC

Variables		Hazard Ratio (95% CI)	P-value
Age at time of diagnosis (years)**		1.05 (1.03 - 1.06)	0.000
Tumor localization	Glottis*	-	-
	Supraglottis	3.03 (1.48 - 6.26)	0.003
T-stage	1A and 1*	-	-
	1B	2.27 (1.29 - 3.99)	0.004
	2	1.93 (1.51 - 2.97)	0.003
	3	3.89 (2.41 - 6.28)	0.000
	4A	4.95 (2.93 - 8.36)	0.000
N-stage	0*	-	-
	1	1.35 (0.90 - 2.04)	0.150
	≥2	1.13 (1.63 - 2.40)	0.013
Treatment given	Yes*	-	-
	No	12.80 (6.94 - 23.60)	0.000
Pack years**		1.006 (1.000 - 1.012)	0.069
Total ACE-27 score	0 (none)*	-	-
	1 (mild)	1.33 (0.93 - 1.89)	0.121
	2 (moderate)	1.57 (1.07 - 2.30)	0.019
	3 (severe)	3.32 (2.18 - 5.08)	0.000
Body Mass Index**		0.97 (0.94 - 0.99)	0.033
Weight loss	< 5%*	-	-
	≥ 5%	1.38 (0.99 - 1.90)	0.054
Anemia	No*	-	-
	Yes	1.41 (1.05 - 1.90)	0.024

*: reference value, **: hazard ratio per unit or year increase.

DISCUSSION

In this study, we demonstrated that anemia and low BMI both have a significant impact on overall survival independently of the presence of comorbidity as measured by the ACE-27 index. Addition of both anemia and BMI to an existing prognostic model showed a borderline significant improvement of the predictive power of the model.

Two recent reviews discussing the relationship between BMI and survival concluded that BMI had a J- or a U-shaped relationship with mortality. Both excessively low and high BMI resulted in a worse prognosis.[13,14] In contrast, univariate survival analysis of BMI in our study showed an inverse relationship with overall survival.

We observed a J-shaped relationship between BMI and comorbidity. The difference between this J-shaped relationship and the inverse relationship between BMI and survival

suggest that the impact of BMI on survival was independent of comorbidity. This was confirmed by our multivariate analysis, in which we adjusted for comorbidity . The cause for this may be related to the obesity paradox.[15] In this paradox the presence of high BMI is a favorable prognostic factor for patients with chronic disease, such as malignancies.

In a review on the impact of BMI on survival of head and neck malignancies, published in 2015, BMI was also inversely correlated with survival.[10] This review stated that patients with high BMI may have higher nutritional reserves. This may be beneficial during treatment, as treatment (such as chemo-radiation therapy) may lead to less intake. Furthermore, Hollander et al. mentioned that pre-existing illnesses and weight loss could be a confounder to the presence of low BMI.[10] However, they did not report on the prevalence of these variables. After we took into account both the ACE-27 comorbidity index and weight loss, BMI still had a significant negative association with overall survival. Gama et al. also found that BMI remained a predictor of overall survival after adjusting for presence of comorbidity.[16]

In the ACE-27 comorbidity index, BMI above 38 is classified as a moderate comorbidity. No comorbidity score is given to underweight patients. This is not in accordance with the inverse relationship between BMI and survival found in our study. In addition, no multiplicative interaction term was found between BMI and the ACE-27 comorbidity index. Therefore, our results suggest that the ACE-27 comorbidity index may be sub-optimal in evaluating the prognosis of patients with LSCC.

According to literature, 20.2% of all patients with head and neck cancer have ≥5% weight loss within 1 month or ≥10% in the last 6 months at the time of diagnosis.[17] In our study 15% of all patients had ≥5% weight loss in the 6 months prior to diagnosis. Patients with malignancies of the glottis are known to show less than 10% weight loss at the time of diagnosis.[17] This group made up nearly two thirds of our study, which may explain the lower prevalence of weight loss. Weight loss is known to have higher prevalence at the time of treatment initiation then at the time of diagnosis (32.2% versus 20.2%) and prevalence shows high discrepancy between early and late stages of disease.[17]

In univariate survival analysis moderate and severe weight loss had a similar influence on overall survival. Langius et al. reported that weight loss has a negative impact on prognosis in both univariate and multivariate analysis. However, they had not taken comorbidity or BMI into account.[18] In a similar study which included HNSCC from all tumor sites, Datema et al. reported that weight loss (classified as >10% of total body weight) was a predictive factor for overall survival in univariate but was no longer significant in multivariate survival analysis.[19] This is in line with our study, as after performing multivariate survival analysis in our study, the association between ≥ 5% weight loss and survival was no longer signifi-

cant after multivariate survival analysis. However, we measured weight loss at the time of diagnosis, while prevalence is known to be higher at the start of treatment.[17] Therefore, new studies should be performed in order to further investigate the relationship between weight loss, BMI and survival in both LSCC and head and neck cancer in general.

Prevalence of anemia in this study was far lower than reported in several recent studies. Hoff et al. reported a prevalence of 41.3% and Baumeister et al. reported 53.7%, compared to 15.4% in our study.[20,21] Several differences in study population may explain this finding. Hoff et al. reported significantly more regional metastases (N+; prevalence of 54.8% versus 16.1%) and more T3 and T4 tumors (52.4% versus 47.6%). Furthermore, his study population consisted of 69.8% pharyngeal- and 30.2% supraglottic malignancies.[20] Baumeister et al. focused on oropharyngeal malignancies, and reported 66% moderate and severe comorbidity versus 36.9% in our study.[21] In our study comorbidity, T- and N-stage have shown to be significantly correlated with the presence of anemia. Furthermore, Baumeister et al. included low hematocrit levels and low red blood cell count as independent variables for defining anemia, which could also explain the discrepancy in prevalence of anemia.[21]

During univariate analysis, presence of anemia proved to have a significantly negative influence on overall survival. This association persisted after adjusting for other known predictors of overall survival, including T-stage, N-stage and comorbidities. The hazard ratio of anemia (HR = 1.41) is very similar to the hazard ratio of a moderate comorbidity (HR = 1.57). Reasoning behind the impact of anemia on overall survival may be because of the impact of anemia on treatment, but also because it may be a marker for underlying tumor cachexia.

While we did not have data on patient treatment, anemia is known to decrease the effectiveness of radiotherapy.[11] It results in a reduction of overall survival and local control of head and neck cancer treated with radiotherapy.[22-24] Furthermore, blood transfusions or administration of erythropoietin do not improve prognosis.[22,25,26] However, transfusions temporarily lessen symptoms such as fatigue and breathlessness, and therefore may improve quality of life. [27]

A study on the effect of anemia on outcomes of surgical treatment of oral SCC also reported that a decrease in pre-treatment hemoglobin levels lead to an increase in local recurrence and lymph node metastasis.[28] A second study, in which all 336 patients received surgical therapy and only 30% received post-operative radiotherapy, concluded that patients who were not anemic have better overall survival and relapse-free survival. [9]

Finally, anemia is known to be one of the diagnostic criteria for tumor cachexia, along with weight loss.[17,29] Presence of tumor cachexia is known to negatively impact overall survival and thus may be an underlying confounder.[17,29] Therefore, more research is needed on the role of tumor cachexia and anemia as independent variables for survival.

Our research group develops prognostic models for head and neck carcinoma since 2001, with the intention to help reduce the gap between scientific studies and clinical practice.[30] The prognostic model created in the current study showed to be able to predict overall survival with LSCC fairly good, with a reasonably good C-statistic of 0.79. The C-statistic was a slight improvement over the previous model by Datema et al. and van der Schroeff et al. (C-statistic of 0.77 with our LSCC data). The previously published model of Datema et al. for head and neck cancer originating from all head and neck regions, reported a lower C-statistic of 0.73.[5] The article published by Van der Schroeff et al., again reporting on a prognostic model for all head and neck HNSCC, stated a C-statistic ranging from 0.76 for 1 year survival to 0.69 for 5 year survival.[6] Reason for the higher C-statistic in the current study may be due to the homogenous population of only laryngeal carcinomas.

All data on BMI and weight loss was scored at the time of diagnosis. It is known that prevalence of weight loss at the time of diagnosis is lower than at the start of treatment, which also affects patient BMI.[17] This may have led to an overestimation of patient BMI and as a result an underestimation of the impact low BMI has on patient survival. In a similar way, presence of anemia may be affected by the time delay between diagnosis and start of treatment. However, more research is needed to confirm this.

Study strengths and limitations

A major strength of this study is the large consecutive patient population with only a minimum of missing data. Also this study is first in describing the relationship between BMI, general comorbidities and survival in patients with LSCC.

However, there are several limitations to this study. First of all, we did not take socio-economic status (SES) into account. Several studies have shown the importance of SES in head and neck carcinoma.[31-35] However, the variables marital status, comorbidities, smoking status and TNM stage at time of diagnosis are related to SES.[31-33] Several studies show that after taking all these variables into account during multivariate analysis, survival of LSCC is no longer associated with SES.[34,35]

A second study limitation is the moment of data inclusion. All data on anemia, BMI and weight loss was scored at the time of diagnosis. It is known that prevalence of weight loss at the time of diagnosis is lower than at the start of treatment. Not only does this affect

weight loss, it also affects patient BMI.[17] This may have led to an overestimation of patient BMI and, as a result, an underestimation of the impact low BMI has on patient survival. Presence of anemia may also be affected by the time delay between diagnosis and start of treatment.

Additionally, anemia is known to be one of the diagnostic criteria for tumor cachexia, along with weight loss.[17,29] Presence of tumor cachexia is known to negatively impact overall survival and thus may be an underlying confounder.[17,29] Therefore, more research is needed on the role of tumor cachexia and anemia as independent variables for survival.

CONCLUSION

Our study has shown that the presence of anemia and low BMI have an independent negative effect on overall survival of LSCC. During patient counseling, physicians should take presence of anemia and low BMI into account before deciding on patient treatment proposal. The new improved prognostic model presented in this study, which includes both anemia and BMI, may help to improve estimation of prognosis in patients suffering from laryngeal carcinomas. Future research should focus on updating prognostic models for all head and neck cancer localizations with inclusion of anemia and BMI.

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