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**MAIN ARTICLE**

# Comparison of the Adult Comorbidity Evaluation 27 and the Charlson Comorbidity indices in patients with laryngeal squamous cell carcinoma

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## Abstract

*Objective*: This study aimed to compare the prognostic impact of comorbidity grading by the Adult Comorbidity Evaluation 27 index and the Charlson Comorbidity Index on the five-year overall and disease-specific survival in patients undergoing surgery for laryngeal squamous cell carcinoma.

*Methods*: The impact of comorbidity and other factors on survival was examined retrospectively in a group of 177 patients with previously untreated tumour stage one to four laryngeal squamous cell carcinoma surgically treated at the Clinic of Otorhinolaryngology and Maxillofacial Surgery, Clinical Centre of Serbia, between 2000 and 2003. The Cox proportional hazard model was used to identify independent prognostic factors.

*Results*: On univariate analysis, comorbidity had an impact on prognosis regardless of which index was used. On multivariate analysis, the significant predictors of patients' five-year overall and disease-specific survival were tumour–node–metastasis stage and comorbidity as graded by the Adult Comorbidity Evaluation 27 index.

*Conclusion*: The Adult Comorbidity Evaluation 27 index is a more reliable predictor of survival than the Charlson Comorbidity Index in patients with laryngeal squamous cell carcinoma.

**Key words:** Laryngeal Neoplasms; Squamous Cell Carcinoma; Comorbidity; Survival Analysis

## Introduction

Comorbidities are diseases or conditions that coexist with the disease of interest. They can influence the treatment choice and the rate of complications, and can confound the survival analysis. Multiple studies have shown that cancer patients with comorbid conditions have worse outcomes than those without.[1–3]

Ideally, an index or scale used to measure comorbid illness should reduce a patient's known medical burden to a single number on a severity scale, which can then be used to stratify patients for analysis. Comorbidity indices firstly identify the present comorbid diseases, and secondly apply weight or severity ratings for these diseases. Weightings are based on the relative risk of dying, and are used to indicate that not all comorbid conditions have the same impact on the total comorbidity burden. A variety of comorbidity scoring indices have been developed, each with its own individual characteristics and validity, since the introduction of the Cumulative Illness Rating Scale in 1968.[4]

Comorbidity instruments can be divided into two groups: general and disease-specific.

Instruments that measure the burden of comorbidity across a wide range of index conditions are usually referred to as general comorbidity instruments. Examples of general comorbidity instruments are the Cumulative Illness Rating Scale, the Charlson Comorbidity Index, the Index of Coexistent Disease and the Klabunde Index.[2,4–6]

Instruments specifically developed to measure the overall severity of comorbidity for a particular index disease are referred to as disease-specific instruments. Examples of these instruments are the Kaplan–Feinstein Index, the Adult Comorbidity Evaluation 27 index, the Washington University Head and Neck Comorbidity Index, and the Head and Neck Cancer Index.[1,7–13]

Several studies have investigated the impact of comorbidity in laryngeal cancer using the Charlson Comorbidity Index and/or the Adult Comorbidity Evaluation 27 index, all of which have demonstrated a significantly poorer survival rate in the presence of comorbidity.[9–11,14]

The Charlson Comorbidity Index is a multi-item, summative scale with a list of 19 conditions which

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are weighted.[2] The following 10 ailments, found within the index, are weighted as level one: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcerative disease, mild liver disease and diabetes. The following six conditions are weighted as level two: hemiplegia, moderate or severe renal disease, diabetes mellitus with end-organ damage, any tumour, leukaemia, and lymphoma. The only condition weighted as level three is moderate or severe liver disease. Finally, metastatic solid tumours and acquired immunodeficiency syndrome are weighted as level six. The total Charlson Comorbidity Index score is calculated by adding together the weighted scores for each comorbid condition. Charlson Comorbidity Index grades one, two and three are assigned to scores of one to two, three to four, and five or more, respectively. If an individual has one or two conditions of an assigned weight of one, that person would be given a grade of one (i.e. mild comorbidity). An individual with a condition weighted five or more would be given a grade of three. A score of five or more is considered high, and usually represents extremely poor health and a low chance of survival. Charlson suggested that, in longitudinal studies, both age and comorbidity should be taken into account as predictors of death. The age-adjusted comorbidity index is calculated by adding one point to the Charlson Comorbidity Index for each decade of age after the fifth decade of life.

The Adult Comorbidity Evaluation 27 index (a modification of the original Kaplan–Feinstein Index) includes 27 different comorbid ailments, comprising disorders of various organ systems (e.g. cardiovascular, respiratory, gastrointestinal, renal, endocrine, neurological and immunological), psychiatric and rheumatological disorders, previous or coexistent malignancy, substance abuse, and body weight status.[7] Comorbid conditions and ailments are categorised according to the degree of organ decompensation, and a prognostic classification of mild, moderate or severe is given. Many patients have multiple diseases and comorbid ailments which contribute to their overall comorbidity ranking. This ranking is based on a severity scale ranging from one to three. Cases with two or more moderate ailments within different organ systems are considered severe and given a grade of three, whereas a mild ailment in a single organ system would result in a grade of one.

The current study was performed to compare the prognostic impact of comorbidity graded by the Charlson Comorbidity Index (a general comorbidity index) and the Adult Comorbidity Evaluation 27 index (a disease-specific comorbidity index) on the five-year overall survival and disease-specific survival of patients undergoing surgical treatment with curative intent, alone or in combination with post-operative radiotherapy, for laryngeal squamous cell carcinoma.

## Materials and methods

### *Study design and patients*

The impact of comorbidity and other factors on survival was examined retrospectively in a group of 177 patients with previously untreated tumour (T) stage $T_1$ to $T_4$ laryngeal squamous cell carcinoma. These patients were treated for newly diagnosed laryngeal squamous cell carcinoma between 1 January 2000 and 31 December 2003 at the Clinic of Otorhinolaryngology and Maxillofacial Surgery, Clinical Centre of Serbia. Five-year survival data were available for 153 patients (86.4 per cent).

The following criteria were required for inclusion in the study: a histologically confirmed diagnosis of squamous cell carcinoma; the absence of previous oncological treatment for this primary tumour; and surgical treatment with curative intent, alone or as part of a multidisciplinary treatment approach (with post-operative radiotherapy). Surgical treatment of neck disease included selective neck dissection for node (N) stage $N_0$ or $N_1$ disease, and modified radical neck dissection or radical neck dissection for nodal disease (stage $N_+$). Indications for post-operative radiotherapy included locally advanced tumours, positive surgical margins and nodal metastasis. We excluded from the study any patient who refused prescribed treatment, who had inadequate documentation, or who had unresectable or metastatic cancer.

The study data were obtained from medical records, tumour registry abstracts and pathology reports. Comorbidity data were extracted from patients' medical records by two investigators working independently, and entered in a database. After independent grading, patients' grades were compared and any discrepancies between the raters resolved by discussion, resulting in the final review grade. To investigate the quality of our comorbidity data, inter-observer reliability and intra-observer reliability were calculated.

We reviewed each patient's demographic data, tumour–node–metastasis (TNM) staging, type of treatment and treatment outcomes. The outcome measures comprised the five-year overall survival and disease-specific survival rates. The TNM staging system was based on the criteria established in 2010 by the American Joint Committee on Cancer.[15] The outcome was determined by assessing the presence or absence of cancer at the time of the last contact and the patient's current status (alive or dead). For patients who had died, the cause was determined from death certificates, family contacts or tumour registry abstracts.

### *Statistical methods*

The weighted kappa statistic was calculated to assess the intra-observer and inter-observer reliability of our retrospective comorbidity data. For this purpose, the first researcher coded all patients twice in a period of six months, and the second researcher coded comorbidity only once during the review of patients' notes. A

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kappa statistic greater than 0.80 was interpreted as a good level of agreement.[16] Spearman's correlation coefficient was used to examine correlation between the two comorbidity grading systems (i.e. the Adult Comorbidity Evaluation 27 index and the Charlson Comorbidity Index). When Spearman's rank correlation coefficient was greater than 0.7, the association between ranks was interpreted as strong.

Survival analysis was performed using the Kaplan–Meier method and the log-rank test for group comparison of survival curves. The Cox proportional hazards regression model was chosen to identify independent prognostic factors. In the case of non-parametric data, the Mann–Whitney and Kruskal–Wallis tests were performed in order to assess the differences between the groups.

Statistical analysis was performed using commercially available software (Statistical Product and Service Solutions for Windows, version 17.0; SPSS Inc, Chicago, Illinois, USA).

## Results and analysis

The distribution of patients' demographics, tumour characteristics and treatment details, for the study population of 177 patients (162 men and 15 women), is shown in Table I. The mean (±standard deviation) age of the population studied was 58.7 (±9.6) years, with ages ranging from 18 to 81 years. Most of the patients were male (91.5 per cent) and were current smokers (94.3 per cent) and drinkers (68.6 per cent) at the time of diagnosis. Pathological grading of squamous cell carcinoma was recorded in 164 cases, with well differentiated lesions present in 70 (42.7 per cent) cases, moderately differentiated in 80 (48.8 per cent) and poorly differentiated in 14 (8.5 per cent).

TABLE I
PATIENT DEMOGRAPHICS, TUMOUR CHARACTERISTICS AND TREATMENT DETAILS*

| Variable | Category | Patients | |
|---|---|---|---|
| | | *n* | % |
| Age group | <60 y | 88 | 49.7 |
| | ≥60 y | 89 | 50.3 |
| Gender | Male | 162 | 91.5 |
| | Female | 15 | 8.5 |
| Laryngeal Ca subsite | Supraglottis | 60 | 33.9 |
| | Glottis | 117 | 66.1 |
| T stage | $T_1$ | 48 | 27.1 |
| | $T_2$ | 48 | 27.1 |
| | $T_3$ | 56 | 31.7 |
| | $T_{4a}$ | 25 | 14.1 |
| N stage | $N_0$ | 156 | 88.1 |
| | $N_+$ | 21 | 11.9 |
| TNM stage | I | 48 | 27.1 |
| | II | 44 | 24.9 |
| | III | 52 | 29.4 |
| | IVA | 31 | 17.5 |
| | IVB | 2 | 1.1 |
| Supraglottal Ca TNM stage | I | 2 | 3.3 |
| | II | 18 | 30.0 |
| | III | 21 | 35.0 |
| | IVA | 18 | 30.0 |
| | IVB | 1 | 1.7 |
| Glottal Ca TNM stage | I | 46 | 39.3 |
| | II | 26 | 22.2 |
| | III | 31 | 26.5 |
| | IVA | 13 | 11.1 |
| | IVB | 1 | 0.9 |
| Treatment | Surgery | 109 | 61.6 |
| | Surgery & RT | 68 | 38.4 |

*$n$ = 177. Y = years; Ca = carcinoma; T = tumour; N = node; $N_+$ = neck disease; M = metastasis; RT = post-operative radiotherapy

Of the 117 glottic tumours, 46 (39.3 per cent) were staged $T_1$, 26 (22.2 per cent) were $T_2$, 31 (26.5 per cent) were $T_3$ (four of these patients had neck disease ($N_1$)), and 14 (12.0 per cent) were $T_4$ (four of these patients had neck disease, as follows: $N_{2b}$, $n = 2$; $N_{2c}$, $n = 1$; and $N_3$, $n = 1$). Of the 60 supraglottic tumours, two (3.3 per cent) were staged $T_1$, 22 (36.7 per cent) were $T_2$ (four of these patients had neck disease: $N_1$, $n = 1$; $N_{2b}$, $n = 2$; and $N_{2c}$, $n = 1$), 25 (41.7 per cent) were $T_3$ (six of these patients had neck disease: $N_1$, $n = 1$; $N_{2a}$, $n = 1$; $N_{2b}$, $n = 2$; and $N_{2c}$, $n = 2$), and 11 (18.3 per cent) were $T_4$ (three of these patients had neck disease: $N_1$, $n = 2$; and $N_3$, $n = 1$). There was a significant difference ($p < 0.001$) between the TNM stage distribution of glottic primary tumours (61.5 per cent were early stage tumours and 38.5 per cent were late stage) and supraglottic primary tumours (33.3 per cent were early stage tumours and 66.7 per cent were advanced stage).

Regarding treatment options, 109 (61.6 per cent) patients were treated with surgery only, while the remaining 68 (38.4 per cent) received post-operative radiation therapy. Laryngeal preservation surgery was performed in 104 patients (58.7 per cent), while total laryngectomy was performed in 73 (41.3 per cent). The commonest types of partial laryngectomy were open cordectomy ($n = 28$, 15.8 per cent), standard partial vertical laryngectomy ($n = 22$, 12.4 per cent), hemilaryngectomy ($n = 21$, 11.9 per cent), standard or extended supraglottic laryngectomy ($n = 18$, 10.2 per cent), anterior frontal or frontolateral laryngectomy ($n = 9$, 5.0 per cent), and supracricoid partial laryngectomy with cricohyoidopexy ($n = 6$, 3.4 per cent).

Kappa-weighted statistics revealed a good level of intra-rater and inter-rater agreement regarding Charlson Comorbidity Index and Adult Comorbidity Evaluation 27 index grades. For the Charlson Comorbidity Index data, the kappa value was 0.93 ($p < 0.001$) for intra-observer reliability and 0.88 ($p < 0.001$) for inter-observer reliability. For the Adult Comorbidity Evaluation 27 index, the intra-observer and inter-observer reliability was 0.88 ($p < 0.001$) and 0.82 ($p < 0.001$), respectively. The Spearman correlation coefficient, comparing the Charlson Comorbidity Index and the Adult Comorbidity Evaluation 27 index, was 0.75 ($p < 0.001$).

In our group of patients with laryngeal squamous cell carcinoma, the most frequent comorbid ailments were related to the cardiovascular, respiratory and

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TABLE II
COMORBIDITY DISTRIBUTION: CCI *VS* ACE-27

| System | CCI | | | | ACE-27 | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr 1 | Gr 2 | Gr 3 | Total | Gr 1 | Gr 2 | GR 3 | Total |
| Cardiovascular | 12 | 17 | 10 | 39 | 44 | 29 | 12 | 85 |
| Respiratory | 11 | 12 | 4 | 27 | 8 | 10 | 7 | 25 |
| Gastrointestinal | 5 | 6 | 3 | 14 | 3 | 5 | 6 | 14 |
| Endocrine | 2 | 5 | 2 | 9 | 1 | 5 | 3 | 9 |
| Neurological | 0 | 5 | 0 | 5 | 1 | 3 | 1 | 5 |
| Renal | 0 | 0 | 1 | 1 | 2 | 0 | 1 | 3 |
| Rheumatological | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 2 |
| Substance abuse | – | – | – | – | 5 | 6 | 4 | 15 |
| Psychiatric | – | – | – | – | 1 | 0 | 0 | 1 |
| Body weight | – | – | – | – | 0 | 0 | 1 | 1 |

CCI = Charlson Comorbidity Index; ACE-27 = Adult Comorbidity Evaluation 27 index; Gr = grade; – = category not included

gastrointestinal systems (Table II). The number of patients assessed as having comorbid illness was 71 (40.1 per cent) according to the Charlson Comorbidity Index and 118 (66.7 per cent) according to the Adult Comorbidity Evaluation 27 index (Tables III and IV). Of those patients with comorbid illness, the proportion having illness in more than one body system was 25.4 per cent according to the Charlson Comorbidity Index and 27.1 per cent according to the Adult Comorbidity Evaluation 27 index.

There was no difference in patients' comorbidity distribution or severity, comparing older versus younger patients and male versus female patients (Tables III and IV). According to the Charlson Comorbidity Index, 106 patients (59.9 per cent) had no comorbidity, 27 (15.3 per cent) had mild comorbidity, 34 (19.2 per cent) had moderate comorbidity and 10 (5.6 per cent) had severe comorbidity. According to the Adult Comorbidity Evaluation 27 index, 59 patients (33.3 per cent) had no comorbidity, 66 (37.3 per cent) had mild comorbidity, 35 (19.8 per cent) had moderate comorbidity and 17 (9.6 per cent) had severe comorbidity. Our results showed a statistically significant difference in the degree of comorbidity of patients with supraglottic versus glottic carcinoma ($p < 0.01$). In patients with supraglottic carcinoma, moderate to severe comorbidity was present in 33.3 and 40.0 per cent according to the Charlson Comorbidity Index and the Adult Comorbidity Evaluation 27 index, respectively. In patients with glottic carcinoma, moderate to severe comorbidity was present in 20.5 and 23.9 per cent according to the Charlson Comorbidity Index and the Adult Comorbidity Evaluation 27 index, respectively.

The median follow-up time for the 177 patients was 53.0 months (range, one to 60 months). At the time of the last follow-up appointment, 99 patients (55.9 per cent) were disease-free, eight (4.5 per cent) were alive with disease, 57 (32.2 per cent) had died of their cancer and 13 (7.3 per cent) had died of other causes.

The five-year overall and disease-specific survival rates for the various comorbidity classifications are shown in Table V. The five-year overall survival rate for the entire group of patients was 58.4 per cent, and the disease-specific survival rate was 65.4 per cent. Patients with glottic tumours had a significantly higher five-year overall survival rate compared with those with supraglottic tumours ($p = 0.029$). There was a statistically significant difference ($p < 0.001$)

TABLE III
COMORBIDITY DISTRIBUTION: CCI*

| Variable | Category | None | | Mild | | Moderate | | Severe | | Statistics |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *n* | % | |
| Age group | <60 y | 54 | 61.4 | 26 | 29.5 | 6 | 6.8 | 2 | 2.3 | $z = -1.917$, $p=0.055$† |
| | ≥60 y | 52 | 58.4 | 1 | 1.1 | 28 | 31.5 | 8 | 9.0 | |
| Gender | Male | 99 | 61.1 | 24 | 14.8 | 30 | 18.5 | 9 | 5.6 | $z = -1.041$, $p=0.298$† |
| | Female | 7 | 46.7 | 3 | 20.0 | 4 | 26.7 | 1 | 6.6 | |
| Laryngeal Ca subsite | Supraglottis | 26 | 43.4 | 14 | 23.3 | 17 | 28.3 | 3 | 5.0 | $z = -2.842$, $p=0.004$† |
| | Glottis | 80 | 68.4 | 13 | 11.1 | 17 | 14.5 | 7 | 6.0 | |
| TNM stage | I | 31 | 64.6 | 8 | 16.7 | 7 | 14.6 | 2 | 4.1 | $X_2=6.491$, $p = 0.090$‡ |
| | II | 26 | 59.1 | 7 | 15.9 | 9 | 20.5 | 2 | 4.5 | |
| | III | 35 | 67.3 | 5 | 9.6 | 11 | 21.2 | 1 | 1.9 | |
| | IV | 14 | 42.4 | 7 | 21.2 | 7 | 21.2 | 5 | 15.2 | |

*$n = 177$. †Mann–Whitney test; ‡Kruskal–Wallis test. CCI = Charlson Comorbidity Index; y = years; Ca = carcinoma;TNM = tumour–node–metastasis

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TABLE IV
COMORBIDITY DISTRIBUTION: ACE-27*

| Variable | Category | None | | Mild | | Moderate | | Severe | | Statistics |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *n* | % | |
| Age group | <60 y | 36 | 40.9 | 29 | 33.0 | 12 | 13.6 | 11 | 12.5 | $z = -1.527$, $p = 0.127$† |
| | ≥60 y | 23 | 25.8 | 37 | 41.7 | 23 | 25.8 | 6 | 6.7 | |
| Gender | Male | 57 | 35.2 | 59 | 36.4 | 31 | 19.1 | 15 | 9.3 | $z = -1.566$, $p = 0.117$† |
| | Female | 2 | 13.3 | 7 | 46.7 | 4 | 26.7 | 2 | 13.3 | |
| Laryngeal Ca subsite | Supraglottis | 13 | 21.7 | 23 | 38.3 | 13 | 21.7 | 11 | 18.3 | $z = -2.921$, $p = 0.003$† |
| | Glottis | 46 | 39.3 | 43 | 36.8 | 22 | 18.8 | 6 | 5.1 | |
| TNM stage | I | 18 | 37.5 | 20 | 41.7 | 8 | 16.7 | 2 | 4.1 | $X^2 = 12.005$, $p = 0.007$‡ |
| | II | 14 | 31.8 | 15 | 34.1 | 14 | 31.8 | 1 | 2.3 | |
| | III | 20 | 38.5 | 22 | 42.3 | 7 | 13.5 | 3 | 5.7 | |
| | IV | 7 | 21.2 | 9 | 27.3 | 6 | 18.2 | 11 | 33.3 | |

*$n = 177$. †Mann–Whitney test; ‡Kruskal-Wallis test. ACE-27 = Adult Comorbidity Evaluation 27 index; y = years; Ca = carcinoma; TNM = tumour–node–metastasis

in the five-year overall and disease-specific survival rates of patients with differing TNM stages.

Patients who had no or mild comorbidity according to the Adult Comorbidity Evaluation 27 index had significantly better five-year overall and disease-specific survival rates than patients with moderate to severe comorbidity ($p < 0.01$).

We analysed the predictive factors for five-year overall survival and disease-specific survival. Table VI summarises these prognostic factors' hazard ratios and degree of significance following univariate Cox proportional hazard regression analysis.

The next step was to examine how these variables performed simultaneously in a multivariate Cox regression analysis. We created two multivariate Cox regression models, one for each of the two comorbidity indices. This analysis indicated that the TNM staging and the Adult Comorbidity Evaluation 27 comorbidity grading were significant predictors of patients' five-year overall survival and disease-specific survival. Multivariate analysis indicated that the Charlson Comorbidity Index comorbidity grading was a significant prognostic factor for five-year overall survival, along with the TNM stage, but was not an independent prognostic

TABLE V
FIVE-YEAR OVERALL AND DISEASE-SPECIFIC SURVIVAL RATES BY VARIABLE

| Variable | Category | OS | | DSS | |
|---|---|---|---|---|---|
| | | % | *p** | % | *p** |
| Age group | <60 y | 60.0 | 0.905 | 63.2 | 0.430 |
| | ≥60 y | 56.9 | | 67.6 | |
| Gender | Male | 58.5 | 0.953 | 65.7 | 0.943 |
| | Female | 57.8 | | 62.6 | |
| Laryngeal Ca subsite | Supraglottis | 45.1 | 0.029 | 54.3 | 0.074 |
| | Glottis | 64.8 | | 70.5 | |
| T stage | $T_1$ | 86.3 | <0.001 | 88.2 | <0.001 |
| | $T_2$ | 57.8 | | 69.6 | |
| | $T_3$ | 45.7 | | 54.7 | |
| | $T_{4a}$ | 33.4 | | 35.7 | |
| TNM stage | I | 86.3 | <0.001 | 88.2 | <0.001 |
| | II | 63.1 | | 71.0 | |
| | III | 48.0 | | 57.8 | |
| | IV | 26.4 | | 32.2 | |
| Treatment | Surgery | 65.0 | 0.062 | 71.2 | 0.089 |
| | Surgery & RT | 47.2 | | 55.4 | |
| CCI comorbidity | None | 66.1 | 0.001 | 71.8 | 0.240 |
| | Mild | 53.0 | | 55.2 | |
| | Moderate | 48.4 | | 57.5 | |
| | Severe | 24.0 | | 50.8 | |
| ACE-27 comorbidity | None | 70.1 | <0.001 | 76.5 | <0.001 |
| | Mild | 61.6 | | 68.0 | |
| | Moderate | 48.4 | | 56.8 | |
| | Severe | 29.4 | | 36.8 | |
| Total population† | | 58.4 | | 65.4 | |

*Log-Rank test. †$n = 177$. OS = five-year overall survival; DSS = five-year disease-specific survival; y = years; Ca = carcinoma; T = tumour; TNM = tumour–node–metastasis; RT = post-operative radiotherapy; CCI = Charlson Comorbidity Index; ACE-27 = Adult Comorbidity Evaluation 27 index

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TABLE VI
PROGNOSTIC FACTORS FOR FIVE-YEAR OVERALL AND DISEASE-SPECIFIC SURVIVAL: HAZARD RATIOS AND SIGNIFICANCE*

| Variable | OS | | DSS | |
|---|---|---|---|---|
| | HR (95%CI) | *p* | HR (95%CI) | *p* |
| Age ( ≥60 y) | 1.03 (0.64–1.64) | 0.906 | 0.81 (0.48–1.38) | 0.433 |
| Gender (female) | 0.98 (0.42–2.25) | 0.953 | 1.03 (0.41–2.59) | 0.943 |
| Laryngeal Ca subsite (glottis) | 0.60 (0.37–0.96) | 0.032 | 0.62 (0.36–1.06) | 0.079 |
| TNM stage | 2.14 (1.68–2.74) | <0.001 | 2.21 (1.67–2.93) | <0.001 |
| Treatment (surgery) | 1.25 (0.99–1.58) | 0.066 | 1.26 (0.96–1.64) | 0.093 |
| CCI comorbidity | 1.42 (1.12–1.80) | 0.003 | 1.29 (0.98–1.70) | 0.064 |
| ACE–27 comorbidity | 1.59 (1.24–2.04) | <0.001 | 1.63 (1.22–2.16) | <0.001 |

*Univariate Cox proportional hazard regression analysis. OS = five-year overall survival; DSS = five-year disease-specific survival; HR = hazard ratio; CI = confidence interval; y = years; Ca = carcinoma; TNM = tumour–node–metastasis; CCI = Charlson Comorbidity Index; ACE-27 = Adult Comorbidity Evaluation 27 index

factor for five-year disease-specific survival, although TNM stage was (Table VII).

## Discussion

### *Comorbidity distribution*

Paleri *et al.* studied patients with laryngeal squamous cell carcinoma using the Adult Comorbidity Evaluation 27 index, and found that 116 (64.4 per cent) of 180 patients with $T_1$–$T_4$ cancer had comorbid illnesses, the majority cardiovascular (44 per cent) or respiratory (24 per cent).[17] One quarter (25.8 per cent) of these 116 patients had illnesses in more than one body system. Comorbidity was absent in 35.5 per cent of patients, mild in 31.1 per cent, moderate in 22.2 per cent and severe in 11.1 per cent.

Chen *et al.* studied comorbidity using the same instrument in 182 patients all with advanced laryngeal squamous cell carcinoma (i.e. stage $T_3$ or $T_4$).[11] Comorbidity was absent in 36 per cent of patients, mild in 29 per cent, moderate in 23 per cent and severe in 12 per cent.

Castro *et al.* assessed comorbid illness in 90 patients with laryngeal cancer (stages $T_1$ to $T_4$), using the two instruments used in our study. Comorbidity classifications were as follows: for the Adult Comorbidity Evaluation 27 index, none in 21.1 per cent, mild in 62.2 per cent, moderate in 7.8 per cent and severe in 8.9 per cent; and for the Charlson Comorbidity Index, none in 34.4 per cent, mild in 53.4 per cent, and moderate or severe in 12.2 per cent.[10]

Sabin *et al.* applied the Charlson Comorbidity Index to a cohort of 152 patients with laryngeal cancer (stages $T_1$ to $T_4$).[14] The Charlson comorbidity score was low for 126 patients (83 per cent) and high for 26 (17 per cent).

Our rates of comorbidity, graded by the Adult Comorbidity Evaluation 27 index and the Charlson Comorbidity Index, were similar to those of other authors.[10,11,14,17] A total of 66.7 per cent of our patients had comorbidity, and 27.1 per cent of them had more than one comorbid disease at the time of presentation. During data collection, we found that some patients had other ailments that could possibly affect their survival but which could not be included in the Charlson Comorbidity Index scoring system. These conditions were hypertension, coronary artery disease, arrhythmias, venous disease, pancreatitis, alcohol abuse, psychiatric illness and obesity. As a result, these patients' Charlson Comorbidity Index scores were lower than would have been the case if these conditions had been included in the scoring system.

### *Comorbidity, age and laryngeal subsite*

Chen *et al.* demonstrated a significant relationship between comorbidity and patient age.[11] Patients older

TABLE VII
MULTIVARIATE COX MODEL* RESULTS FOR FIVE-YEAR OVERALL AND DISEASE-SPECIFIC SURVIVAL

| Model | Variable | OS | | DSS | |
|---|---|---|---|---|---|
| | | HR (95%CI) | *p* | HR (95%CI) | *p* |
| I | CCI comorbidity | 1.28 (1.01–1.62) | 0.045 | – | – |
| | TNM stage | 2.06 (1.61–2.63) | <0.001 | 2.21 (1.67–2.93) | <0.001 |
| II | ACE-27 comorbidity | 1.37 (1.07–1.76) | 0.012 | 1.39 (1.05–1.84) | 0.020 |
| | TNM stage | 2.00 (1.56–2.56) | <0.001 | 2.05 (1.55–2.72) | <0.001 |

*Final step for backward Wald method. OS = five-year overall survival; DSS = five-year disease-specific survival; HR = hazard ratio; CI = confidence interval; CCI = Charlson Comorbidity Index; – = no significant prediction; TNM = tumour–node–metastasis; ACE-27 = Adult Comorbidity Evaluation 27 index

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than 70 years had a significantly higher burden of comorbidity than younger patients. Paleri *et al.* reported significantly greater comorbidity in individuals older than 65 years compared with younger individuals.[9] In our study, patients 60 years of age or older did not have a significantly higher comorbidity burden than younger patients.

Paleri *et al.* also reported, for the first time, a significantly higher comorbidity burden in patients with supraglottic cancers rather than glottic tumours.[9] Notably, this study found that comorbidity had a greater and statistically more significant impact on survival outcome than did TNM stage. Similarly, our study found that patients with supraglottic carcinoma had a statistically significantly higher comorbidity burden ($p < 0.01$) than those with glottic carcinoma.

### *Comorbidity and survival*

The relationship of comorbidity and survival in laryngeal cancer patients has been investigated in several studies.

Sabin *et al.* reported that patients with high-grade comorbidity had significantly poorer survival than those with low-grade comorbidity.[14]

Chen *et al.* also found a significant correlation between comorbidity and both five-year survival and overall survival.[11] Patients with either moderate or severe comorbidity had significantly worse overall survival and worse five-year survival, compared with those with no or mild comorbidity. However, there was no significant difference between the two comorbidity groups as regards disease-specific survival.

Singh *et al.* also demonstrated that the median disease-free interval and overall survival were significantly poorer for patients with advanced comorbidity compared with those with low-grade comorbidity.[18]

Our findings are in accordance with those of Singh *et al.*, and indicate that frequent follow up is especially important for patients with advanced comorbidity to allow earlier detection of cancer recurrence.[19]

### *Which comorbidity index for laryngeal carcinoma patients?*

Singh *et al.* compared the Charlson Comorbidity Index to the modified Kaplan–Feinstein Index in a cohort of patients younger than 45 years who had head and neck cancer.[18,19] Both indices were found to be prognostic indicators of disease-specific survival. However, the Charlson Comorbidity Index was more easily applied to retrospective data than the modified Kaplan–Feinstein Index.

While the Charlson Comorbidity Index grading system merely requires information on the presence of disease in the various body systems, significantly more data are needed for Adult Comorbidity Evaluation 27 index grading (e.g. test results and detailed historical information). The Charlson Comorbidity Index does not take into account the severity of a given comorbid condition, but merely its presence or absence.[20]

Both general and disease-specific comorbidity indices provide important prognostic information.

In our study, we noted that our disease-specific index (the Adult Comorbidity Evaluation 27 index) performed better than our general index (the Charlson Comorbidity Index). Our findings are in accordance with Hall *et al.*, who compared four validated indices with very different methodologies (the Charlson Comorbidity Index, Cumulative Illness Rating Scale, Kaplan–Feinstein Index and Index of Coexistent Disease), and concluded that the Kaplan–Feinstein Index was the best index for the patient population because it came closest to creating three statistically distinct strata of comorbid illness.[21]

In contrast, Piccirillo *et al.* studied two disease-specific comorbidity indices (the Washington University Head and Neck Comorbidity Index and the Head and Neck Cancer Index) and two general comorbidity indices (the Charlson Comorbidity Index and the Klabunde Index), and found that all performed equally well in their cohort of elderly patients with head and neck cancer.[22]

Based on our results, we propose that the Adult Comorbidity Evaluation 27 index is the best instrument with which to determine comorbidity in laryngeal carcinoma patients.

### *Comorbidity as independent prognostic factor for laryngeal cancer survival*

Castro *et al.* conducted a retrospective study of 90 patients with stage $T_1$–$T_4$ laryngeal squamous cell carcinoma. Their multivariate analysis identified comorbidity and TNM stage as independent prognostic factors for overall survival.[10]

Chen *et al.* demonstrated the significance of comorbidity in the treatment and outcomes of 182 patients with $T_3$ or $T_4$ laryngeal squamous cell carcinoma.[11]Analysis of predictive factors for disease-specific survival, five-year survival and overall survival revealed that comorbidity was an independent predictor of five-year and overall survival but not of disease-specific survival. Disease-specific survival was predicted by conventional TNM staging.

Montero *et al.* evaluated the influence of comorbidity as a prognostic factor in 99 patients affected by locally advanced laryngeal and/or hypopharyngeal cancer and receiving a combined protocol treatment.[23] Multivariate analysis identified TNM stage, neoadjuvant chemotherapy response and comorbidity as independent prognostic factors for overall survival (risk ratio = 1.55) and disease-specific survival (risk ratio = 1.44).

Our study's multivariate analysis identified TNM stage and comorbidity, as defined by the Adult Comorbidity Evaluation 27 index, as independent prognostic factors for five-year overall and disease-specific survival. For each additional degree of

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comorbidity, the risk of death by any cause increased by 37 per cent and the risk of death by laryngeal tumour increased by 39 per cent.

Apart from its direct effect on survival, severe comorbidity can also have a prognostic impact by altering therapy.[10] Consequently, the presence of prognostic comorbidity introduces the concept of personalised medicine to facilitate successful cancer treatment.[24]

- **Tumour–node–metastasis (TNM) stage and comorbidity are the most important prognostic factors for laryngeal cancer patient survival**
- **In this study, the Adult Comorbidity Evaluation 27 index registered more comorbid ailments than the Charlson Comorbidity Index**
- **Adult Comorbidity Evaluation 27 index grade and TNM stage were independent prognostic factors for five-year overall and disease-specific survival**
- **Charlson Comorbidity Index grade and TNM stage were independent prognostic factors only for five-year overall survival**
- **The former index is more reliable than the latter in predicting laryngeal cancer patient survival**

In the future, multicentre studies which do not assess comorbidity will be open to accusations of weakness, as they will not have considered the possibility that comorbidity may have influenced treatment outcomes.[25] Comorbidity has more prognostic importance in patients in whom the prognostic impact of the tumour is small. In cases in which the tumour is advanced or aggressive and the prognosis is poor, comorbidity information is less important. In the near future, comorbidity could become a standard complement to the TNM staging system. Further studies are necessary to confirm the influence of comorbidity on cancer survival.

## Conclusion

Our study identified comorbidity, as graded by the Adult Comorbidity Evaluation 27 index, and TNM staging as significant predictors of five-year overall and disease-specific survival in patients with laryngeal squamous cell carcinoma. The Adult Comorbidity Evaluation 27 index was a more reliable predictor of survival than the Charlson Comorbidity Index in this patient group.

We suggest that future prospective studies should include comorbidity as a predictive factor for patient survival. Furthermore, we propose that the Adult Comorbidity Evaluation 27 index should be the instrument of choice for grading comorbidity in patients with laryngeal squamous cell carcinoma.

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