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ORIGINAL ARTICLE

Risk Factors for Early Mortality in Head and Neck Cancer Patients Undergoing Definitive Chemoradiation

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ABSTRACT

Introduction: *Head and neck cancer (HNC) afflicts >16,000 people in Hong Kong annually. Non-operative treatment for HNC typically involves radiotherapy (with or without concurrent systemic therapy) and is associated with significant acute toxicity. Demography, tumour factors, and co-morbidities each influence treatment outcome and prognosis, but their role in predicting 90-day mortality is less well-known.*

Methods: *Demographic, clinical, and co-morbidity data of 725 non-metastatic HNC patients (9.4% stage I/II, 90.6% stage III/IV), who had undergone definitive radiotherapy from 1 January 2016 to 1 March 2020 were collected. Predictors for 90-day mortality were evaluated by simple and multivariable logistic regression.*

Results: *We report a 4.6% 90-day mortality rate. Age >60 years (odds ratio [OR] = 3.453, 95% confidence interval [CI] = 1.195-9.928; p = 0.022), Eastern Cooperative Oncology Group performance status (OR = 2.184, 95% CI = 1.071-4.454; p = 0.032) and pre-treatment haemoglobin level (OR = 0.764, 95% CI = 0.596-0.979; p = 0.034) were significant predictors of 90-day mortality on multivariable analysis. Of the eight co-morbidity scores studied, the Adult Comorbidity Evaluation–27 (ACE-27) [OR = 2.177, 95% CI = 1.397-3.393; p = 0.001] and the Taipei Medical University–concurrent chemoradiotherapy Mortality Predictor Score (TMU-CCRT) [OR = 1.501, 95% CI = 1.134-1.986; p = 0.004) were the most significant predictors of 90-day mortality.*

Conclusion: *Both clinical factors and co-morbidities predict early mortality in HNC patients. ACE-27 and TMU-CCRT are appropriate for co-morbidity assessment in relation to early mortality. Further studies to develop prospective models that identify accurately patients at risk of early mortality during treatment are necessary.*

Key Words: *Comorbidity; Drug therapy; Head and neck neoplasms; Mortality; Prognosis*

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中文摘要

接受根治性放化療的頭頸癌患者早期死亡的危險因素

徐譽文、張嘉文、周重行、黃錦洪

引言：香港每年有超過16,000人罹患頭頸癌。頭頸癌的非手術治療通常包括放射治療（聯合或不聯合全身性治療），與顯著急性毒性相關。人口統計學、腫瘤和共病症都會影響治療結果和預後，但它們在預測90天死亡率的作用則鮮為人知。

方法：收集2016年1月1日至2020年3月1日期間接受根治性放療的725例非轉移性頭頸癌患者（I/II期佔9.4%、III/IV期佔90.6%）的人口統計學、臨床和共病症數據。通過簡易及多變量邏輯迴歸評估90天死亡率的預測因子。

結果：90天死亡率為4.6%。60歲以上（優勢比3.453，95%置信區間 = 1.195-9.928；p = 0.022）、ECOG表現狀態（優勢比2.184，95%置信區間 = 1.071-4.454；p = 0.032）和治療前血紅蛋白水平（優勢比0.764，95%置信區間 = 0 596-0.979; p = 0.034）是多變量分析中90天死亡率的重要預測因子。在研究的八種共病症評分中，成人共病症評估27量表（ACE-27；優勢比2.177，95%置信區間 = 1.397-3.393; p = 0.001）及臺北醫學大學同步放化療死亡率預測評分（TMU-CCRT；優勢比1.501，95%置信區間 = 1.134-1.986；p = 0.004）是90天死亡率的最重要預測因子。

結論：臨床因素和共病症均可預測頭頸癌患者的早期死亡率。ACE-27和TMU-CCRT適用於與早期死亡率相關的共病症評估。需要進一步研究發展更全面模式以準確識別治療期間有早期死亡風險的患者。

INTRODUCTION

Radiotherapy and chemotherapy are two of the mainstays of treatment for head and neck cancer (HNC).[1] Radiotherapy of HNC may cause mucositis, dermatitis, or dysphagia, whereas addition of concomitant chemotherapy increases the risk of myelosuppression, nausea and vomiting, neurotoxicities, and nephrotoxicities. Although these typically improve within 6 months after treatment in most patients,[2] some patients succumb to these toxicities shortly after treatment.[3-5] The United Kingdom introduced a 5% 90-day mortality rate following radical radiotherapy in HNC as a quality metric.[6,7]

Treatment outcomes in HNC are influenced by a range of patient and disease factors. Co-morbidity is a known independent prognosticator for survival in HNC.[8,9] There are several co-morbidity scores available with known prognostic significance in HNC, some of which are suitable for registry-based and retrospective assessment.[8,10]

The most commonly utilised co-morbidity indices are the Charlson Comorbidity Index (CCI)[11] and the Adult Comorbidity Evaluation–27 (ACE-27).[12] These have both been validated in HNC patients.[10,13] An ACCI (age-adjusted Charlson Comorbidity Index) is another established co-morbidity score derived from the CCI and assigns 1 additional point per decade over 40 years of age up to 4 points.[14] Although validated in HNC,[15,16] it is less widely used than CCI and ACE-27.

There are several assessment tools designed specifically for HNC patients. The HN-CCI (head and neck comorbidity index score)[17] and the HNCA (head and neck cancer index)[18] are both adapted from the CCI. The WUHNCI (Washington University Head and Neck Comorbidity Index) contains seven weighted conditions. It was shown to improve prognostication over a multivariable regression model comprising age, sex, race, symptom stage, and TNM stage.[19] The Simplified Comorbidity Score (SCS) includes seven co-morbid conditions and smoking status.[20] It was originally developed for lung cancer patients, but Göllnitz et al[21] demonstrated its prognostic value in HNC along with other co-morbidity scores. The Taipei Medical University–concurrent chemoradiotherapy (TMU–CCRT) Mortality Predictor Score is the only

co-morbidity score developed for prediction of 90-day mortality post radical chemoradiotherapy in locally advanced HNC patients.[3]

We sought to assess the 90-day mortality rate after radical radiotherapy, with or without concurrent systemic treatment, to identify significant risk factors for early mortality and to assess the predictive value of different co-morbidity scores.

METHODS

Patient Cohort

All 1649 consecutive patients treated with radiotherapy for HNC from 1 January 2016 to 1 March 2020 at a single tertiary cancer centre were screened for eligibility. The Figure shows the flowchart for screening. Patients who were planned for radiotherapy with curative intent, with or without systemic treatment, as primary treatment for non-metastatic primary HNC from all sites and stages were included. To eliminate the effect of postoperative recovery and chemotherapy before or after radiotherapy, those who had surgery, and those who received neoadjuvant or adjuvant chemotherapy with primary treatment, were excluded. We also excluded patients who received a planned radiation dose of <66 Gy to the planning target volume. Patients who were diagnosed with lymphoma, skin malignancies, sarcomas or thyroid malignancies were excluded. All 725 patients included in our analysis had received at least 6 months of follow-up post completion of primary treatment at time of analysis.

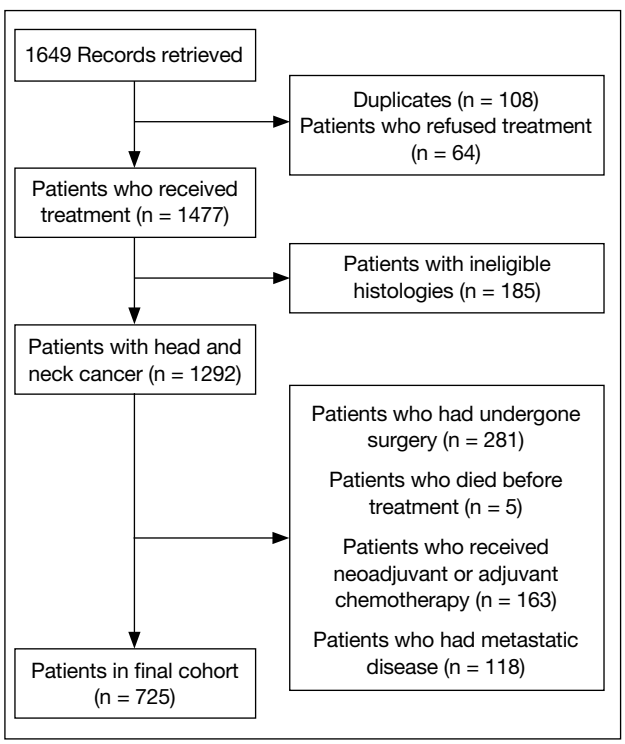

Figure. Flowchart of case selection.

Treatment Technique

Radiotherapy to the head and neck region was administered via intensity-modulated radiotherapy, volumetric mediated arc therapy, or in the case of nasopharyngeal cancers (NPC), TomoTherapy. Radiotherapy doses up to 70-72 Gy in 33 fractions for NPC and up to 70 Gy in 35 fractions for squamous HNC were prescribed. Concurrent chemoradiotherapy regimens included weekly cisplatin 40 mg/m^2; cisplatin 100 mg/m^2 given once every 3 weeks; or cetuximab 400 mg/m^2 1 week before radiotherapy and 250 mg/m^2 in subsequent weekly doses until completion of radiotherapy.

Data Extraction and Calculation of Co-morbidity Scores

In our study, early mortality was defined as 135 days from start of radiotherapy as a surrogate for 90-day mortality post radical radiotherapy, assuming a maximum planned overall treatment time of 45 days.[4]

Manual review and data extraction were performed for each patient. Demographic information, including age, sex, body weight and height, smoking history, and alcohol use were extracted. Eastern Cooperative Oncology Group (ECOG) performance status was documented. Tumour site, histology and staging, the results of baseline swallowing assessment, treatment details including treatment technique, dose, and concurrent systemic therapy were logged. Disruptions or unplanned events warranting medical attention during treatment, including unplanned feeding tube insertion, admission, or need for adaptive replanning of radiotherapy were recorded. Start and end dates of radiotherapy, last date of follow-up, and date and cause of death were recorded.

Baseline laboratory values including haemoglobin, white cell count, platelet count, albumin, creatinine, calcium, and lactate dehydrogenase were retrieved. Symptom score at presentation, scored as the number of items present from the following list: dysphagia, otalgia, weight loss and presence of neck mass, was calculated.[22]

Patient records were reviewed for co-morbidities comprising seven of the eight co-morbidity scores

mentioned — CCI, ACCI, HN-CCI, SCS, WUHNCI, HNCA and TMU-CCRT. The calculation of ACE-27 was assessed directly from electronic medical records. The full list of co-morbidities assessed is shown in Table 1.

Statistical Analysis

The full cohort was analysed for demographic information. Univariate analysis was performed using the Chi-square test for categorical data and the Mann-Whitney *U* test for continuous or ordinal data to compare the 90-day mortality and survival groups. Multivariable logistic regression was performed to evaluate the effect of different variables on 90-day mortality after chemoradiotherapy, controlling for other covariates. A p value <0.05 was taken as significant.

RESULTS

In total, among 1649 consecutive patients, 1292 were treated with radiotherapy for HNC during the study period from 1 January 2016 to 1 March 2020 (Figure). After exclusions for prior surgery (n = 281), neoadjuvant or adjuvant chemotherapy (n = 163), metastatic disease (n = 118), or death before treatment (n = 5), finally 725 patients were included in our cohort and received ≥6 months of follow-up after completion of radiotherapy at time of analysis (Figure).

The median age at diagnosis was 59 years. A total of 19.6% were aged >70 years, and 76.3% were male. Lifetime smokers and drinkers made up 55% and 37% of cases, respectively. The most common tumour site was nasopharynx (70.2%), followed by larynx (13.9%), oropharynx (7.6%), oral cavity (3.7%), hypopharynx (2.9%), and other sites (1.6%). Locally advanced disease (stage III/IV) made up 90.6% of cases. A total of 74.1% received chemotherapy and radiotherapy. The median follow-up was 23.1 months as of 30 November 2020 (Table 2).

In all, 33 out of 725 patients (4.6%) did not survive beyond 90 days from the end of treatment. Of these, 14 patients (42.4%) died due to pneumonia or sepsis, nine (27.3%) developed sudden cardiac arrest. Four died due to distant relapse, and five died due to other causes including acute kidney injury, pneumoperitoneum, or deterioration after early termination of treatment. Cause of death was not available for one patient.

Poorer radiation tolerance was noted in the 90-day mortality group, with significantly higher rates of

Table 1. Co-morbidity information.*

Characteristic	Early mortality group (n = 33)	Survival group (n = 692)	p Value
Co-morbidity scores, median (IQR)			
CCI	1 (0-4)	0 (0-1)	<0.001
HNCCI	1 (0-1.5)	0 (0-1)	<0.001
WUHNCI	1 (0-1.5)	0 (0-0)	0.062
ACCI	4 (2-6)	2 (1-3)	<0.001
SCS	2 (2-6.5)	2 (1-8)	0.509
ACE-27	2 (1-3)	0 (0-1)	<0.001
HNCA	1 (0-1)	0 (0-0)	<0.001
TMU-CCRT	2 (1-3.5)	1 (0-1)	<0.001
Lifetime co-morbid conditions			
Cardiac ischaemia and myocardial infarction	3 (9.1%)	40 (5.8%)	0.432
Chronic pulmonary disease	1 (3.0%)	28 (4.0%)	0.771
Congestive heart failure	1 (3.0%)	8 (1.2%)	0.342
Ulcer	3 (9.1%)	40 (5.8%)	0.432
Peripheral vascular disease	1 (3.0%)	6 (0.9%)	0.214
Mild liver disease	2 (6.1%)	45 (6.5%)	0.920
Cerebrovascular disease	7 (21.2%)	37 (5.3%)	<0.001
Diabetes mellitus	9 (27.3%)	91 (13.2%)	0.022
Dementia	3 (9.1%)	7 (1.0%)	<0.001
Hemiplegia	6 (18.2%)	7 (1.0%)	<0.001
Moderate or severe renal disease	6 (18.2%)	36 (5.2%)	0.002
Diabetes with end-organ damage	3 (9.1%)	6 (0.9%)	<0.001
Non-head-and-neck malignancy	2 (6.1%)	37 (5.3%)	0.859
Leukaemia	0	2 (0.3%)	0.757
Lymphoma	0	3 (0.4%)	0.705
Moderate or severe liver disease	1 (3.0%)	6 (0.9%)	0.214
Metastatic non-head-and-neck malignancy	0	3 (0.4%)	0.705
AIDS	0	3 (0.4%)	0.705
Hypertension	13 (39.4%)	215 (31.1%)	0.314
Arrhythmia	2 (6.1%)	16 (2.3%)	0.176
Hyperlipidaemia	6 (18.2%)	115 (16.6%)	0.814
Autoimmune disease	0	14 (2.0%)	0.409
Tuberculosis	6 (18.2%)	25 (3.6%)	<0.001
Asthma	0	13 (1.9%)	0.427
Pulmonary embolism	0	0	-
Severe valvular cardiomyopathy	0	3 (0.4%)	0.705
Co-morbidity diagnosis in past year			
Electrolyte disturbance	2 (6.1%)	9 (1.3%)	0.029
Chronic pulmonary disease	2 (6.1%)	16 (2.3%)	0.176
Diabetes mellitus	9 (27.3%)	85 (12.3%)	0.012
Congestive heart failure	1 (3.0%)	6 (0.9%)	0.214
Urinary tract infection	2 (6.1%)	3 (0.4%)	<0.001
Pneumonia	6 (18.2%)	8 (1.2%)	<0.001
Gastrointestinal bleeding	1 (3.0%)	13 (1.9%)	0.639
Cerebrovascular disease	1 (3.0%)	6 (0.9%)	0.214
Sepsis	4 (12.1%)	10 (1.4%)	<0.001
Hemiplegia	2 (6.1%)	5 (0.7%)	0.002
Moderate severe renal disease	7 (21.2%)	29 (4.2%)	<0.001
Leukaemia	0	2 (0.3%)	0.757
Metastatic non-head-and-neck malignancy	0	3 (0.4%)	0.705

Abbreviations: ACCI = age-adjusted CCI; ACE-27 = Adult Comorbidity Evaluation–27; AIDS = acquired immunodeficiency syndrome; CCI = Charlson Comorbidity Index; HNCA = head and neck cancer index; HNCCI = head and neck CCI; IQR = interquartile range; SCS = Simplified Comorbidity Score; TMU-CCRT = Taipei Medical University–concurrent chemoradiotherapy Mortality Predictor Score; WUHNCI = Washington University Head and Neck Comorbidity Index.
* Data are shown as No. (%), unless otherwise specified.

adaptive radiotherapy replanning (30.3% vs. 13.0%, p = 0.005), feeding tube insertion during treatment (21.2% vs. 9.2%, p = 0.024), radiotherapy suspension (36.4% vs. 5.9%, p < 0.001) and unplanned admissions (51.5% vs. 5.9%, p < 0.001).

A total of 57% of cases had at least one co-morbid condition (Table 1). The 90-day mortality group had higher median scores across all of the co-morbidity indices except SCS. A history of stroke (21.2% vs. 5.3%, p < 0.001), diabetes (27.3% vs. 13.2%, p = 0.022) or diabetes with complications (9.1% vs. 0.9%, p < 0.001), dementia (9.1% vs. 1.0%, p < 0.001), hemiplegia (18.2% vs. 1.0%, p < 0.001) and moderate-to-severe renal disease (18.2% vs. 5.2%, p = 0.002) were more common in the 90-day mortality group. Within 1 year of diagnosis of HNC, electrolyte disturbance (6.1% vs. 1.3%, p = 0.029), sepsis (12.1% vs. 1.4, p < 0.001), pneumonia (18.2% vs. 1.2%, p < 0.001), and urinary tract infections (6.1% vs. 0.4%, p < 0.001) were more common in the 90-day mortality group.

Results of simple logistic regression analysis are shown in Table 3. Multivariable logistic regression analysis (Table 4) identified age >60, ECOG performance status, and pre-treatment haemoglobin as significant independent predictors of 90-day mortality. Of the co-morbidity indices investigated, when controlled for clinical parameters, only ACE-27 and TMU-CCRT remained significant on multivariable regression analysis.

DISCUSSION

Our study found a 4.6% 90-day post-treatment mortality rate, which was within the 5% cut-off per the National Institute of Clinical Excellence and the Scottish Cancer Taskforce recommendations.[6,7] Other real-world cohorts have reported early mortality rates of 5% to 18%.[3,23,24] Historical randomised controlled trials, which reported early mortality rates of 1% to 5%, defined the early mortality period differently, ranging from 30 days from end of treatment to 90 days from the start of treatment.[25-27] As in our cases, the addition of chemotherapy in these studies was associated with a lower early mortality rate, although this difference is likely attributable to confounding due to selection of fitter patients for more intensive treatment.[25-27]

Early mortality in NPC is less studied compared to locally advanced squamous cell carcinomas. Despite sharing similar radiotherapy doses, organs at risk and systemic

Table 2. Patient demographics and treatment details.*

Characteristic	Early mortality group (n = 33)	Survival group (n = 692)	p Value
Age, median (IQR), y	66.3 (61.0-76.6)	58.7 (49.1-67.2)	0.006
<40	1 (3.0%)	62 (9.0%)	
40-49	0	129 (18.6%)	
50-59	6 (18.2%)	181 (26.2%)	
60-69	15 (45.5%)	189 (27.3%)	
70-79	5 (15.2%)	89 (12.9%)	
≥80	6 (18.2%)	42 (6.1%)	
Sex			0.109
Women	4 (12.1%)	168 (24.3%)	
Men	29 (87.9%)	524 (75.7%)	
BMI, median (IQR), kg/m^2	21.6 (18.0-23.7)	23.6 (21.0-25.8)	0.001
<18.5	7 (21.2%)	49 (7.1%)	
Not underweight	23 (69.7%)	642 (92.8%)	
Missing	3 (9.1%)	1 (0.1%)	
Smoking status			0.763
Never smoker	14 (42.4%)	301 (43.5%)	
Ex-smoker	10 (30.3%)	169 (24.4%)	
Smoker	9 (27.3%)	211 (30.5%)	
Missing	0	11 (1.6%)	
Drinking status			0.409
Non-drinker	15 (45.5%)	282 (40.8%)	
Ex-drinker	5 (15.2%)	42 (6.1%)	
Drinker	9 (27.3%)	214 (30.9%)	
Missing	4 (12.1%)	154 (22.3%)	
ECOG performance score			<0.001
0	1 (3.0%)	82 (11.8%)	
1	14 (42.4%)	531 (76.7%)	
2	13 (39.4%)	52 (7.5%)	
3	4 (12.1%)	5 (0.7%)	
4	0	1 (0.1%)	
Missing	1 (3.0%)	21 (3.0%)	
Primary tumour site			0.001
Nasopharynx	16 (48.5%)	493 (71.2%)	
Oral cavity	4 (12.1%)	23 (3.3%)	
Oropharynx	5 (15.2%)	50 (7.2%)	
Hypopharynx	3 (9.1%)	18 (2.6%)	
Larynx	3 (9.1%)	98 (14.2%)	
Others	2 (6.1%)	10 (1.4%)	
Group stage			0.059
In situ	0	1 (0.1%)	
I	0	22 (3.2%)	
II	0	46 (6.6%)	
III	15 (45.5%)	412 (59.5%)	
IV	17 (51.5%)	210 (30.3%)	
Missing	1 (3.0%)	1 (0.1%)	
Prevalence of co-morbidity	31 (93.9%)	381 (55.1%)	<0.001
Systemic treatment received	15 (45.5%)	525 (75.9%)	<0.001
Cisplatin 100 mg/m^2 Q3w	7 (21.2%)	304 (43.9%)	
Cisplatin 30 mg/m^2 Q3w	5 (15.2%)	195 (28.2%)	
Cetuximab weekly	2 (6.1%)	19 (2.7%)	
Others	1 (3.0%)	7 (1.0%)	
Adaptive replanning of radiotherapy	10 (30.3%)	90 (13.0%)	0.005
Need for feeding tube insertion	7 (21.2%)	64 (9.2%)	0.024
Radiotherapy suspension	12 (36.4%)	41 (5.9%)	<0.001
Unplanned admission	17 (51.5%)	141 (20.4%)	<0.001

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; Q3w = every 3 weeks.

* Data are shown as No. (%), unless otherwise specified.

Table 3. Results of simple logistic regression analysis for 90-day mortality.

Variable	Odds ratio (95% CI)	p Value
Age	1.057 (1.028-1.088)	<0.001
≥60 (compared with age <60)	4.318 (1.849-10.081)	0.001
Sex (female vs male)	0.430 (0.149-1.241)	0.119
Weight	1.001 (0.999-1.002)	0.275
Body mass index	0.861 (0.775-0.957)	0.006
ECOG performance status	5.313 (3.093-9.125)	<0.001
Smoker	0.974 (0.647-1.467)	0.899
Drinker	1.069 (0.806-1.418)	0.644
Stage	2.599 (1.367-4.938)	0.004
T stage	1.500 (0.912-2.467)	0.110
N stage	0.995 (0.658-1.504)	0.979
Histology		0.350
Squamous cell	Ref	
Undifferentiated carcinoma	0.604 (0.296-1.235)	0.167
Others	1.265 (0.157-10.215)	0.825
Primary tumour site		0.004
Nasopharynx	Ref	
Oral cavity	5.359 (1.659-17.313)	0.005
Oropharynx	3.081 (1.083-8.765)	0.035
Hypopharynx	5.135 (1.372-19.220)	0.015
Larynx	0.943 (0.270-3.299)	0.927
Other sites	6.162 (1.247-30.454)	0.026
Baseline haemoglobin, g/dL	0.586 (0.486-0.708)	<0.001
Baseline white cell count, × 10^9/L	1.054 (0.919-1.208)	0.453
Baseline platelet count, × 10^9/L	1.002 (0.998-1.006)	0.347
Baseline albumin level, g/L	0.859 (0.800-0.921)	<0.001
Baseline creatinine, μmol/L	1.009 (1.001-1.017)	0.031
Baseline calcium level, mmol/L	0.103 (0.002-6.824)	0.288
Baseline lactate dehydrogenase, IU/L	0.993 (0.979-1.007)	0.294
Results of swallowing assessment	1.112 (0.710-1.740)	0.644
Symptom score	2.612 (1.432-4.763)	0.002
Dysphagia	6.687 (2.315-19.309)	<0.001
Otalgia	10.781 (0.952-122.033)	0.055
Neck lump	1.735 (0.787-3.824)	0.172
Weight loss	1.935 (0.242-15.449)	0.534
Co-morbidity indices		
CCI	1.405 (1.201-1.643)	<0.001
HNCCI	2.028 (1.368-3.006)	<0.001
WUHNCI	1.298 (1.090-1.545)	0.003
ACCI	1.383 (1.216-1.572)	<0.001
SCS	0.991 (0.914-1.074)	0.820
ACE-27	3.090 (2.170-4.400)	<0.001
HNCA	2.495 (1.697-3.668)	<0.001
TMU-CCRT	1.979 (1.550-2.526)	<0.001

Abbreviations: 95% CI = 95% confidence interval; ACCI = age-adjusted CCI; ACE-27 = Adult Comorbidity Evaluation–27; CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group; HNCA = head and neck cancer index; HNCCI = head and neck CCI; SCS = Simplified Comorbidity Score; TMU-CCRT = Taipei Medical University–concurrent chemoradiotherapy Mortality Predictor Score; WUHNCI = Washington University Head and Neck Comorbidity Index.

Table 4. Results of multivariable logistic regression analysis for 90-day mortality.

Variable	Odds ratio (95% CI)	p Value
Age >60 y	3.453 (1.195-9.928)	0.022
Body mass index	0.959 (0.866-1.062)	0.423
ECOG performance status	2.184 (1.071-4.454)	0.032
Stage	1.708 (0.872-3.342)	0.118
Primary tumour site		0.640
Baseline haemoglobin, g/dL	0.764 (0.596-0.979)	0.034
Symptom score	1.527 (0.701-3.328)	0.287
Co-morbidity indices*		
CCI	1.054 (0.842-1.321)	0.644
HNCCI	1.220 (0.738-2.016)	0.439
WUHNCI	1.070 (0.857-1.336)	0.548
ACCI†	1.162 (0.968-1.395)	0.106
ACE-27	2.177 (1.397-3.393)	0.001
HNCA	1.514 (0.899-2.551)	0.119
TMU-CCRT†	1.501 (1.134-1.986)	0.004

Abbreviations: 95% CI = 95% confidence interval; ACCI = age-adjusted CCI; ACE-27 = Adult Comorbidity Evaluation–27; CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group; HNCA = head and neck cancer index; HNCCI = head and neck CCI; SCS = Simplified Comorbidity Score; TMU-CCRT = Taipei Medical University–concurrent chemoradiotherapy Mortality Predictor Score; WUHNCI = Washington University Head and Neck Comorbidity Index.

* Co-morbidity scores entered as individual items for multivariable logistic regression analysis.

† Analysed excluding age as a variable.

treatment regimens, NPC, having a different aetiology and clinical course, has been purposely excluded from HNC studies to facilitate long-term prognostic analysis.[3-5] In our study, we included NPC, which made up 69.9% of our cases, due to similarities in primary treatment between NPC and locally advanced HNCs. A similar acute toxicity profile is expected. Our results confirm that the risk of early mortality, after adjusting for different clinical parameters, is not significantly different in patients with squamous cell HNC of other primary sites.[4]

Multivariable logistic regression analysis identified age, ECOG performance status, and haemoglobin levels as significant predictors of early mortality. The effect of age and performance status on prognosis in HNC is well-known.[28] Elderly and frail patients were traditionally excluded from HNC trials,[25-27] although exclusion based on age alone is no longer recommended on the basis of evidence showing no significant differences in objective acute toxicity measurements or late toxicity across different age cut-offs for radical radiotherapy.[29] In patients aged >70 years, however, the addition of chemotherapy

yielded no survival benefit.[1] In our study, we showed that increasing age remained an important predictor for early mortality. Performance status is often used as a proxy for burden of co-morbidity, but other studies have shown that it provides prognostic information independent of co-morbidity.[30,31] The retention of ECOG performance status with certain co-morbidity indices in multivariable logistic regression analysis confirms that both have important implications in predicting early mortality.

In squamous cell HNCs, pre-treatment co-morbidity has consistently been identified as an important independent prognosticator. The role of co-morbidity in NPC is less pronounced, as the Epstein–Barr virus, rather than alcohol and tobacco exposure, is the dominant aetiological factor. Despite this, we found ACE-27 and TMU-CCRT to be independent predictors of early mortality after adjusting for baseline demographic factors. ACE-27 is widely used for co-morbidity assessment across different cancers; it has been shown to predict severe acute toxicity, early mortality, as well as long-term prognosis in HNC.[4,10,32,33] ACE-27 differs from other co-morbidity indices covered here in that it grades overall severity of co-morbidity from 0 (no co-morbidity) to 3 (severe co-morbidity).[12] It also covers a wider scope of co-morbid conditions compared with other co-morbidity indices under review.[10] Currently, it is the recommended standard for recording co-morbidity data in the United Kingdom.[34] TMU-CCRT scores patients for early mortality risk based on stratified age and six other co-morbid conditions.[3] Our results validate the role of TMU-CCRT as a predictor of early mortality in HNC.

Based on median scores in the 90-day mortality and survival groups, ACE-27 was best able to differentiate between severity levels of co-morbidity. An ACE-27 score of 2 corresponds to a moderate level of co-morbidity, while a score of 0 corresponds to no co-morbidity. In contrast, the median scores for TMU-CCRT in the 90-day mortality and survival groups both fell into the low-risk category based on the proposed stratification by Lin et al.[3] This illustrates the need for universally appropriate cut-offs for clinical use. Our review of the current literature found that, apart from ACE-27, different cut-offs have been utilised by different groups to delineate the co-morbidity burden.

Pre-treatment laboratory values are relatively less investigated as prognostic markers.[24] These haematological and biochemical markers may reflect baseline co-morbidity, but not all mechanisms by which they affect survival or treatment outcomes are well understood. In our study, we found that haemoglobin levels below the lower limit of normal was associated with early mortality. In HNC, anaemia is associated with higher recurrence rates and poorer overall survival,[21,35] an effect attributed to decreased efficacy of treatment due to tumour hypoxia and decreased radiosensitivity.[36,37] Other studies have also demonstrated that early mortality was more likely in patients with baseline anaemia.[4] After controlling for other factors, other blood parameters were not correlated with early mortality in our cases.

Sepsis and pneumonia were the most common causes of death among patients who died within 90 days after completing treatment. Radiotherapy to the head and neck often causes acute toxicities such as mucositis, dysphagia, and odynophagia, increasing the risk of aspiration.[38] Eisbruch et al[39] reported aspiration rates up to 65% within 3 months after radiotherapy, while other studies have found aspiration pneumonia rates up to 17.6%.[40] This may be exacerbated by concomitant use of chemotherapy or biologics. Collapse or cardiac events were the second most common, supporting previous work that suggested higher risk of cardiovascular events in cancer patients.[41]

Despite attempts to identify risk factors for early mortality following radical treatment for HNC, the optimal case selection criteria for intensive treatment remains elusive. Substandard treatment is independently associated with poorer survival after adjusting for other factors such as performance status, age, and mild co-morbidity,[42] emphasising the need for comprehensive assessment of fitness for treatment.

There are several limitations to our study. Our data were obtained from a single tertiary cancer centre and consisted of predominantly NPC patients. Analysis from a population-based database and further validation in squamous cell HNC population is necessary to confirm generalisability of our results. Second, information regarding baseline functional status or socioeconomic status was not available from retrospective review of patient records. These are potentially important factors in predicting tolerance to treatment.[43,44] Crucially, although presence of one or more these factors indicates a higher odds of mortality, this does not definitively identify patients who will suffer early death within 90 days after treatment; as such, these factors should not be used to exclude patients from potentially curative treatment. The

best course of action in an individual with multiple risk factors is not known and the formulation of any treatment plan requires careful discussion with the patient.

CONCLUSION

Minimising early treatment mortality is important for optimising outcomes of patients with HNC. The 90-day mortality rate after radical radiotherapy, with or without concurrent systemic treatment, in our cohort was 4.6%. Age, pre-treatment Hb, ECOG performance status, and two co-morbidity indices: ACE-27 and TMU-CCRT, were found to be independent predictors of early mortality. Development of a more comprehensive prediction model from these factors may help with case selection of patients for intensive HNC treatment.

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