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Original Article

Comorbidities: Are they an Independent Predictor for Overall Survival in Oral Cavity Cancer?

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Abstract
Background and Aims: *This study was undertaken to identify the comorbidities which have an independent impact on overall survival (OS) and validate the use of Charlson's comorbidity index (CCI) in patients with oral cavity cancer.*
Methods: *Data of 472 patients (age, sex, tumor site, Tumor (T) stage, Node(N) stage, comorbidities, and treatment) were collected from the case files and CCI score was calculated. Univariate analysis was done and significant variables were subjected to multiple cox regression analysis to identify the possible independent predictive factors of mortality. Cox proportional hazard model to estimate the hazard ratio for overall survival was used. The survival probability was estimated using Kaplan-Meier method and differences of survival were compared by log rank test.*
Results: *A univariate analysis done on the variables affecting mortality showed a $p < 0.2$ for tumor size, nodal spread, hypertension, diabetes, carcinomabuccal mucosa and lower alveolus, age >70 years and CCI score. Nodal spread, hypertension and diabetes mellitus and CCI score were identified as independent predictive factors for overall survival using multiple cox regression. CCI score was identified as an independent predictor of OS using Kaplan Meier analysis. Hypertension (35.2%) was the most common comorbidity in our study population.*
Conclusion: *Comorbidities have a significant impact on the overall survival of oral cavity cancer patients.CCI score is a valid tool to help the clinician assess the prognosis at initially and enable him to choose the optimal treatment which is less toxic to the patient and more cost effective.*
Keywords: *Regression Analysis, Comorbidity, Prognosis, Hypertension, Diabetes Mellitus, Head and Neck Neoplasms.*

Introduction

Comorbidities influence treatment options and outcome of oral cancer. There is a lack of consensus for a treatment protocol in presence of comorbidity in oral cancer. Charlson's comorbidity index (CCI) has been validated for

predicting the outcome from comorbid diseases like heart disease, AIDS or cancer.[1] The CCI contains 19 categories of comorbidity which is assigned a score of 1, 2, 3, or 6 depending on the risk of death. This retrospective cohort study aims to assess the predictive accuracy of CCI score and identify the comorbidities that directly impact overall survival (OS) in oral cavity cancers.

Methods

After obtaining clearance from the Institutional Review Board, data was collected from case files of all oral cavity cancer patients registered in a tertiary cancer institution in the year 2009 and they were followed up as per our institutional protocol. The study was conducted as per declaration of Helsinki. Data of potential risk factors of 472 patients like age, sex, tumor site, T stage, N stage, M status, treatment modalities and comorbidities were collected. Extent of the disease was classified by pathological stages (pTNM); when surgery was not done clinical stages (cTNM) was used. We adapted the Charlson's comorbidity index created by Dr. Mary Charlson which predicts the ten-year mortality for a patient who may have a range of comorbid conditions.[2]Age adjusted CCI score was generated for each patient using an online calculator.(Charlson Comorbidity Index (CCI) – MDCalc https://www.mdcalc.com› charlson-comorbidity-index-cci) (Table1)

All statistical analyses were performed with SPSS 13.The categorical variables like age, gender, comorbidities, tumor site, tumor size, node status, CCI score and treatment modality were reported using frequency and proportions. Univariate analysis was done with these variables and the factors with p value <0.20 was subjected to multiple cox regression analysis to identify the possible independent predictive factors of mortality. Cox Regression is a predictive model for time-to-event data. The living status was taken as the status variable for the cox regression; duration of follow up was taken as time variable. Cox proportional hazard model to estimate the hazard ratio with a confidence interval of 95% for overall survival was used. A p-value < 0.05 was considered to be statistically significant. The survival probability was estimated using Kaplan-Meier method and differences of survival were compared by Log rank test. OS time was defined as the time from first clinical visit to time of last follow up or death from any cause. Conditions with low incidence in the cohort were excluded from the analysis.

Results

Demographic and clinical characteristics of the patients with oral cavity cancer registered in head and neck clinic in the year 2009 are as follows. Study population was predominantlyin the younger age group of ≤ 60 (54%)probably due to early screening programs and newer diagnostic tools and lifestyle changes and 45.4% of the patients were aged ≥ 60 years.OS was 80.9%, 6.6% was the mortality and 12.5% was lost to follow up. Commonest site was carcinoma (ca) tongue (46.2%) and was followed by cabuccal mucosa (23.3%). Ca alveolus (14.6%), cheek (4.4%), floor of mouth (3.8%), palate (2.8%) retromolartrigone (1.7%), maxilla (1.1%), lip (1.1%), oropharynx (0.8%), gingivobulbal sulcus (0.8 %), were the other predominant tumor sites. Majority of patients (81%) were diagnosed in early T_1 & T_2 stages and 19% in T_2&T_4. Node positivity was seen in 43.6%. Nodal status 1& 2 was also associated with higher mortality with a p value of 0.042. 56.4% patients were N_0, 30.9% of all patients were staged N_1 and only 12.7% were N_2. Total 36.4% patients underwent surgery as primary treatment modality. Combination therapy was given for 42.6% and 21% patients had non-surgical treatment (chemotherapy or radiotherapy). The commonest comorbidity was hypertension (35.2%) followed by diabetes (17.8%) and COPD (11%).

A univariate analysis done on the variables affecting mortality showed a p value less than 0.2 for tumor size, nodal spread, hypertension, diabetes, cabuccal mucosa, ca lower alveolus, age

>70 and CCI score. (Table2) These possible predictive factors were subjected to multiple cox regression analysis to identify their significance in OS. Independent predictors of mortality using Multivariate Cox Regression are shown in (Table 3). The independent predictors of time to end mortality were N staging, presence of comorbidities like hypertension, diabetes, cancer lower alveolus and CCI score of patients.

Among the comorbidities hypertension was found as a predictor for mortality with a p value of 0.005. Presence of hypertension was analyzed in relation to tumor size and was found to be an independent predictor for mortality. In our study group hypertension was present in 35.2% and mortality was 12.7% as compared to 4.8% in those without it (p = 0.004). (Table 4)

CCI score was identified as an independent predictor of OS using Kaplan Meier analysis. Total of 176 patients had a CCI score of 2-3, 172 patients 4-5 and only 34 patients with score more than 5. That is, 73.7% patients had a CCI score of 2-5.Mean survival was decreasing as CCI score went up from 2 to 5. This was plotted in Kaplan Meier curve. (Diagram 1). The plot shows that the cumulative survival proportion was very close for CCI score of 2-3 and CCI of 4-5 till sixth year of follow up and after sixth year of follow up cumulative survival function is slightly better for CCI score of 2-3 as compared to CCI score of 4-5. The cumulative survival function for CCI 2-3 and CCI 4-5 was much higher than that of CCI greater than 5. Log-rank test was carried out to compare the survival curves of the three CCI groups. (Table 5) The test statistics (p<0.01) showed that survival curves for three different CCI groups are statistically significant.

Table 1: Scoring used for calculation of age-adjusted Charlson comorbidity index

score	comorbidity
1	Diabetes without end-organ damage
	Myocardial infarction
	Cerebrovascular disease
	Congestive cardiac failure
	Peripheral vascular disease
	Dementia
	Chronic pulmonary disease
	Peptic ulcer disease
	Mild liver disease Age *
2	Diabetes with end organ damage
	Moderate/severe renal disease
	Hemiplegia
	Solid tumor without metastasis
	Leukemia/ Lymphoma
3	Moderate/ severe liver disease
6	Metastatic solid tumor
	AIDS

*Age: For each decade after 50 years a point is added for each decade. <50 years– 0,
age group 50 – 59 has 1 point, age group 60 – 69 has 2 points, 70 – 79 has 3 points and ≥ 80 years has 4 points.

Table 2 Predictors of mortality using Cox Regression (Univariateanalysis)

Variable		HR (95% CI)	p
T Staging (1 - 2)	3 - 4	3.14 (1.44 - 6.85)	0.004
N staging (0)	1	2.79 (1.14 - 6.82)	0.025
	2	3.47 (1.2 - 10.01)	0.022
Hypertension (Absent)	Present	3.08 (1.4 - 6.8)	0.005
Diabetes Mellitus(Present)	Absent	5.2 (0.7 - 38.36)	0.106
Heart disease (Present)	Absent	1.21 (0.16 - 8.93)	0.853
COPD (Present)	Absent	1.41 (0.33 - 5.99)	0.637
Renal dysfunction(Absent)	Present	2.11 (0.28 - 15.65)	0.465
age <50	>=70	2.22 (0.8 - 6.14)	0.125
CCI		1.28 (1.01 - 1.62)	0.041
CCI 2-3	>5	4.14 (1.42 - 12.02)	0.009
Tongue(Yes)	No	1.75 (0.78 - 3.92)	0.176
Lower alveolus (No)	Yes	3.2 (1.39 - 7.37)	0.006
Upper alveolus (No)	Yes	5.14 (1.54 - 17.12)	0.008

*p<0.2 significant

Table 3 Independent predictors of mortality using Multivariate Cox Regression

Variable		HR (95% CI)	P value
N staging (0)	1	2.83(1.14-7)	0.025
	2	4.76(1.62-14.02)	0.005
Hypertension (absent)	present	3.41(1.52-7.66)	0.003
Diabetes Mellitus (present)	absent	12.95(1.66-101.01)	0.015
Lower alveolus (No)	yes	3.36(1.43-7.85)	0.015
CCI		1.44(1.07-1.93)	0.005

P <0.05 significant

Table 4 Comparison of Hypertension based on status for T staging

T staging	HTN	Dead		Live		χ^2	p
		Count	Percent	Count	Percent		
1 - 2	Absent	9	4.1	209	95.9	2.71	0.100
	Present	10	8.5	108	91.5		
3 - 4	Absent	4	7.5	49	92.5	8.35**	0.004
	Present	8	33.3	16	66.7		

P <0.05 significant

Diagram 1.Kaplan-Meier curve showing the Survival function for different CCI Scores

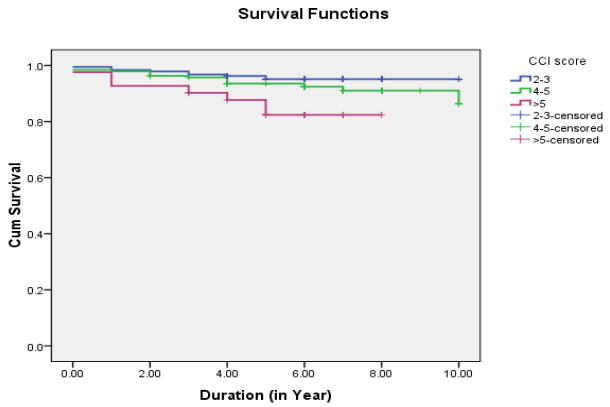

Table 5. Log Rank Test

CCI	Mean survival time	p (Log Rank Test)
2-3	9.64	P <0.01
4-5	9.40	
>5	7.08	

P <0.05 significant

Discussion

Comorbidity is defined as any coexistent disease that is not related to the disease under study which may exist before diagnosis of index disease or occur during the course of disease.[3] These affect the outcome and may increase mortality probably because of adoption of less aggressive treatment protocols.[4] Hence comorbidity can increase mortality in oral cancer patients.[5] Comorbidity indices are useful tools to apply severity ratings for these diseases to help predict outcome. CCI is the most extensively studied comorbidity index for predicting mortality.[6]

Incidence of comorbidities in our study population was 53%. In a population based study using CCI in Thuringia, incidence was around 46%.[7] Piccirillo et al used the ACE- 27 and revealed an incidence of 45%.[8] A study by Rose et al identified comorbidity as an independent risk factor for survival.[9] Chemotherapy related hospitalizations were increased in patients with comorbidity and even completion of treatment became an issue in their presence. [10-12]

Successful treatment of patients with oral cancer is attributed to multidisciplinary treatment strategies that minimize impact of therapy on patient status. Mortality for this disease is coming down because of these developments. OS was 81% in present study probably because 80% of the patients were in early stage (T_1 & T_2) cancer and predominantly younger population (55%). While the tendency of poor prognosis in patients with comorbidity may be due to less aggressive cancer treatment, results showed that there were 10–22% lower 2-year survival rates for patients with severe comorbidity condition given the same disease stage and treatment modality.[13] Therefore, in addition to arriving at decisions on cancer

treatment modality, it is also crucial to emphasize the management of other medical conditions in cancer patients.[13]

Age and sex were not significant predictors of mortality in our study as in similar studies done in other institutions.[5] But male gender, and advanced age were independent prognostic factors of survival in a study in Uganda.[6] Mortality was seen in the age group above 60 years when compared to younger population (20.9% as compared to 11.7%) but not significant statistically.

Patients with ca lower alveolus were found to have higher possibility for mortality with odds of 1.8 though ca tongue was the most common site. There was no significant difference between the cancer location and survival as observed by De Oliveira et al.[14] Honorato et al. showed that cancers located in the hard palate and cheek mucosa presented the worst prognosis.[15]

Most oforal cancer patients are diagnosed in their fifth to seventh decade, an age at which many will have comorbidities.[16] Hypertension has been reported to be the most common comorbidity encountered in patients with malignancy with an incidence of 37% in the study group.[17] In our study group incidence of hypertension was (35.2%) followed by diabetes mellitus and COPD. Hypertension is not a comorbidity assessed in the CCI score. The most commonly confirmed comorbidities inpatients with oral cancer were cardiovascular diseases (congestive heart failure, peripheral artery disease, and hypertension).[18] Moreover, surgery or radiation therapy that involves the head and neck can lead to baroreflex failure and to associated difficult-to-treat labile hypertension and hypertensive crisis.[19] A prospective 14 year mortality follow up study by Dyer et al found a significant association between systolic and diastolic blood pressure and mortality from various cancers, even after appropriate adjustment for age, cholesterol, and smoking.[20]Use of angiogenesis inhibitors in targeted cancer therapy lead to increased prevalence of hypertension and hence it should be diagnosed and managed adequately.[21] Hypertension may be first detected in the outpatient clinic. The need for advanced cardiac testing in a hypertensive cancer patient could be considered in the presence of poor or unknown functional class, risk posed by surgery or associated comorbidities (diabetes mellitus, renal dysfunction), which increase the risk for coronary artery disease.[22]

It is well documented that cancer patients with diabetes have higher mortality than cancer patients without diabetes.[13] A Danish study found that for all cancers combined and diabetes duration of 2 years at cancer diagnosis, patients treated with insulin experienced the highest mortality rate ratios starting from 3.7 for men and 4.4 for women one year after the cancer diagnosis.[13]

Only 20% patients were in T_3 &T_4 stages. Recurrence is high in oral cancer and there is risk for developing subsequent new primary cancers, but the risk of distant recurrence is low.[23] Disease recurrence was not analyzed in our study and is a limitation of this study.

Mortality data was collected from clinical records. Data was incomplete as there were many out of hospital deaths. This is a limitation of the study as cause of death could not be confirmed. In a study, incorporating three nationwide databases they found that patients with severe comorbidity condition (CCI $\geq$ 2) had significantly higher hazard ratios. [24]In our study overall survival was found to be better in CCI score of 2-5 group than in patients with a score more than 5. The hazard ratio corresponding to CCI score was 1.28; it means that, for every increase of one unit in CCI score the relative risk for mortality increases 1.28 times. It may be assumed that the higher comorbid burden interferes with the tumor–host balance, tilting it in favor of the tumor, resulting in a more aggressive disease course.[5] In the present study increasing CCI score was independently associated with increased risk of mortality.

It is now widely accepted that the TNM classification for staging has significant

drawbacks in helping to prognosticate.[5] A statistical technique known as conjunctive consolidation has been used to incorporate comorbidity into the TNM staging system to create a composite staging system. This was first demonstrated for head and neck cancer by Piccirillo et al.[25]. Other investigators have created an innovative ‘‘prognostigram” which uses comorbidity data for prediction of prognosis.[26]

Conclusion

CCI score is a valid tool to help the clinician predict the outcome of treatment in oral cavity cancer population. Standardized comorbidity assessment should be considered as a routine in outpatient clinic registries along with TNM staging of disease. We recommend adding hypertension to comorbidity scoring systems after validation and further research involving multiple centre when calculating the probability of survival in head and neck cancer patients. This will help the clinician to assess the prognosis at initial work up phase, optimize the comorbidities and enable him to choose the optimal treatment which is less toxic to the patient and more cost effective as well.

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Conflicts of interest: There are no conflicts of interest.

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