Title

Comparison of Comorbidity and Frailty Indices in Patients With Head and Neck Cancer Using an Online Tool

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Comparison of Comorbidity and Frailty Indices in Patients With Head and Neck Cancer Using an Online Tool

abstract

Purpose Comorbidity is an independent predictor of mortality and treatment tolerance in head and neck cancer and should be considered with regard to treatment intensification. Multiple previously validated models can be used to evaluate comorbidity and propensity to benefit from intensive treatment, but they have not been directly compared.

Materials and Methods An online tool was developed and used to calculate the Charlson Comorbidity Index (CCI), Adult Comorbidity Evaluation-27 (ACE-27), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Geriatric 8 (G8), Cancer and Aging Research Group (CARG), and Generalized Competing Event (GCE) scores. To assess interrater variability, five evaluators independently calculated scores on a retrospective cohort of 20 patients. Correlation between models as well as age and performance status were calculated from a cohort of 40 patients.

Results The GCE and G8 models had an excellent (intraclass correlation coefficient and Fleiss' kappa ≥ 0.75) degree of interrater agreement. The CCI, ACE-27, CIRS-G, and CARG had a good (intraclass correlation coefficient and Fleiss' kappa 0.6-0.74) degree of interrater agreement. There was statistically significant correlation between models, especially with the CCI, ACE-27, and CIRS-G indices. Increased age was correlated with an increased CCI score and having moderate to severe comorbidity was correlated with the ACE-27 model. Except for the G8 model, the comorbidity indices were not associated with Eastern Cooperative Oncology Group performance status.

Conclusion We developed an online tool to calculate indices of comorbidity in patients with head and neck cancer with a high degree of reproducibility. Comorbidity is not strongly correlated with performance status and should be independently evaluated in patients.

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INTRODUCTION

Comorbidity is an independent predictor of short-term mortality and overall survival in patients with head and neck cancer (HNC).[1-3] Despite their prognostic importance, treatment algorithms for HNC are based on cancer stage, histology, and disease-specific outcomes and do not integrate comorbidity.[4,5] Prior studies have documented rates of at least mild comorbidity in up to 54% of patients presenting with HNC.[6] Risk factors for developing HNC, including tobacco and alcohol use, also place patients at increased risk for noncancer disease. Elderly patients are a particularly challenging population with reduced treatment tolerance, and they represent approximately half of new HNC diagnoses.[7,8] Evaluation of comorbidity is important not only for patients' prognoses but also for predicting their likelihood of benefiting from treatment intensification.[1,9,10]

Adding concomitant cisplatin to radiation therapy has been shown to improve patient survival and is the standard of care for medically fit patients with locally advanced HNC.[5,11,12] However, patients who were age 71 years or older were found to have no survival benefit with the addition of chemotherapy.[12] The lack of survival benefit in elderly patients with HNC is largely attributed to the increased risk of noncancer mortality in this population.[10,13] Compared with clinical trial patients, the general HNC population is less fit with more comorbidities and correspondingly higher rates of noncancer mortality.[2]

In current clinical practice, the decision of whether to intensify treatment in frail or elderly patients with HNC is largely left to a physician's gestalt.[7,14] Performance status (PS) is routinely documented and considered, but it is an inadequate surrogate for evaluating comorbidity.[15,16] Multiple validated models and indices have been

Table 1. Comparison of Input Data for the CCI, ACE-27, CIRS-G, G8, CARG, and GCE Models

Model	Input Variable				
	Cancer Specific	Age	BMI	Performance Status	Medical Comorbidity
CCI	—	Binned in modified CCI	—	—	Binary input on cardiovascular, pulmonary, renal, endocrine, GI, ID, neurologic, and other oncologic disease
ACE-27	—	—	Binary	—	Ordinal input on cardiovascular, pulmonary, renal, endocrine, GI, ID, neurologic, psychiatric, hematologic, and other oncologic disease
CIRS-G	—	—	—	—	Ordinal input on cardiovascular, pulmonary, renal, endocrine, GI, neurologic, psychiatric, ENT, and GU disease
G8	—	Binned	Binary	Self-evaluation of mobility	Categorical input on psychiatric disease and weight loss
CARG	Type of cancer	Binary	—	Binary input on socialization, falls, mobility, RX management	Binary input on kidney function and anemia
GCE	Primary site, N stage, p16 status	Continuous	Binary	ECOG	—

NOTE. Dashes indicate that the covariate is not a component of the respective model. Full versions of each model are available at www.comogram.org.
Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; BMI, body mass index; CARG, Cancer and Aging Research Group; CCI, Charlson Comorbidity Index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; ECOG, Eastern Cooperative Oncology Group; ENT, ear, nose, and throat; G8, Geriatric 8; GCE, Generalized Competing Event; GU, genitourinary; ID, infectious disease; RX, medication.

developed to assess comorbidity or risk of toxicity from treatment, which can be useful in determining whether treatment intensification is appropriate (Table 1). Examples include the Charlson Comorbidity Index (CCI), Adult Comorbidity Evaluation-27 (ACE-27), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Geriatric 8 (G8), Cancer and Aging Research Group (CARG), and Generalized Competing Event (GCE) risk score. An online tool (www.comogram.org) has been created to aggregate these measures in one location to facilitate clinical implementation. This tool is being used in the ongoing NRG-HN004 (ClinicalTrials.gov Identifier: NCT03258554; Radiation Therapy With Durvalumab or Cetuximab in Treating Patients With Stage III-IVB Head and Neck Cancer Who Cannot Take Cisplatin) trial. To evaluate how dependably these measures could be implemented in a clinical setting, we sought to measure correlation and interrater reliability in their individual assessments.

MATERIALS AND METHODS

Existing Models

The CCI was developed to predict the risk of mortality on the basis of the weighted index of various comorbid conditions (Table 1). This model was initially validated in a prospective cohort of patients with breast cancer and has been subsequently validated in multiple other cohorts of patients with or without cancer.[10,16-19] A CCI score ≥ 1 indicates the presence of a major comorbid illness, which significantly increases the risk of noncancer mortality.[9] The ACE-27, a chart-based comorbidity index, was validated in a prospective observational study of nearly 20,000 patients with cancer that showed its correlation with overall survival independent of cancer stage.[6] An ACE-27 score ≥ 1 indicates the presence of any significant comorbid illness. The CIRS-G index was developed to quantify chronic medical illness in geriatric psychiatric patients. High values are correlated with increased mortality, hospitalization rates, and functional disability.[20,21] A CIRS-G score ≥ 4 indicates a moderate level of chronic illness. The G8 model is a screening tool designed to identify frail elderly patients that could benefit from a comprehensive geriatric assessment (CGA), with lower values indicating increasing frailty.[22] A G8 score ≤ 14 is correlated with a greater likelihood of impaired function on a formal CGA. The CARG model was developed to predict the risk of grade 3 to 5 chemotherapy toxicity in a prospective cohort of elderly patients with cancer and was then internally validated.[23] A score of ≥ 15 corresponds to a 30% or higher risk of grade 3 to 5 toxicity according to the CARG model.

Table 2. Patient, Disease, and Comorbidity Characteristics for the Evaluated Patients (N = 40)

Characteristic	No.	%	Median	Range
Sex				
Male	33	82.5		
Female	7	17.5		
Age, years			59	23-77
BMI, kg/m^2			24.8	15.5-49.6
ECOG PS			1	0-2
Cancer primary site				
Oropharynx	15	37.5		
Oral cavity	8	20		
Larynx	7	17.5		
Unknown primary	4	10		
Hypopharynx	3	7.5		
Para-nasal sinus	2	5		
Nasopharynx	1	2.5		
Stage (AJCC 7th edition)				
IV	37	92.5		
T0N2	3			
T0N3	1			
T1N2	5			
T1N3	1			
T2N2	8			
T3N2	6			
T4N0	3			
T4N1	1			
T4N2	8			
T4N3	1			
III	1	2.5		
T1N1	1			
Recurrent	2	5		
rT2N0	2			
ACE-27			1	0-3
G8			12.25	5-17
CARG (%)			11	11-44
CCI			0	0-4
CIRS-G			2	0-10
GCE ω score			0.59	0.23-0.84

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; AJCC, American Joint Committee on Cancer; BMI, body mass index; CARG, Cancer and Aging Research Group; CCI, Charlson Comorbidity Index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; ECOG PS, Eastern Cooperative Oncology Group performance status; G8, Geriatric 8; GCE, Generalized Competing Event.

GCE models are a novel approach to risk-stratifying patients according to their relative hazard for cancer-related events versus competing events (also called the ω ratio).[13,24] In contrast to other approaches, GCE models incorporate both disease-related and competing health factors to identify patients with the highest risk of primary (cancer) versus competing (noncancer) events, who theoretically have the greatest chance to benefit from treatment intensification. Higher ω ratios indicate a higher rate of cancer-specific events compared with competing events, with a

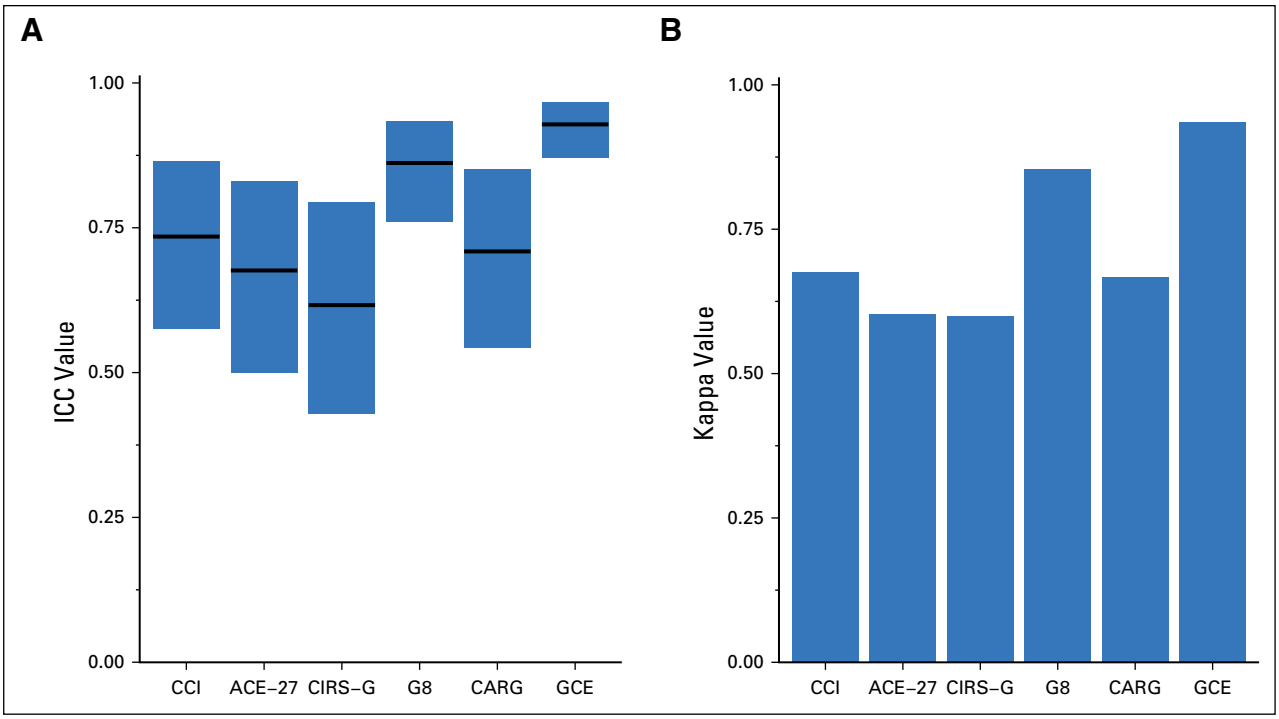

Fig 1. Interrater reliability for comorbidity indices. (A) Intraclass correlation coefficients (ICCs) representing agreement between evaluators for CCI (Charlson Comorbidity Index), ACE-27 (Adult Comorbidity Evaluation-27), CIRS-G (Cumulative Illness Rating Scale for Geriatrics), G8 (Geriatric 8), CARG (Cancer and Aging Research Group), and GCE (Generalized Competing Event) models as continuous or ordinal variables. (B) Fleiss' kappa values representing agreement between evaluators for identifying moderate to severe comorbidity with the CCI, ACE-27, CIRS-G, G8, CARG, and GCE models.

ω ratio of 0.5 corresponding to an equal hazard for primary versus competing events. The GCE risk score used in this tool was trained on a cohort of patients treated on the control arms of three randomized trials: Radiation Therapy Oncology Group RTOG-9003 (ClinicalTrials.gov Identifier: NCT00771641; Fractionated Radiation Therapy in Treating Advanced Squamous Cell Carcinoma of the Head and Neck), RTOG 0129 (ClinicalTrials.gov Identifier: NCT00047008; Chemotherapy and Radiation Therapy With or Without Surgery in Treating Patients With Head and Neck Cancer), and RTOG 0522 (ClinicalTrials.gov Identifier: NCT0026594; Radiation Therapy and Cisplatin With or Without Cetuximab in Treating Patients With Stage III or Stage IV Head and Neck Cancer]). It was then validated in patients treated on the experimental arms of these trials (Mell et al, manuscript submitted for publication). Factors included in the model were age (years), Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index (BMI), primary tumor site, N stage, and p16 status. Patients in the highest GCE risk score quintile with a scaled predicted ω ratio ≥ 0.6 had significantly higher overall survival with treatment intensification compared with patients with a scaled predicted ω ratio < 0.6 (Mell et al, manuscript submitted for publication).

Development and Validation of the Online Tool

A Web-based application was developed to aggregate indices of comorbidity from the CCI, ACE-27, CIRS-G, G8, CARG, and GCE models (www.comogram.org). Threshold values were selected for each model (CCI ≥ 1, ACE-27 index ≥ 1, GCE ω < 0.6, G-8 score ≤ 14, CARG toxicity score ≥ 30%, CIRS-G score ≥ 4) that would indicate a moderate to severe level of comorbidity and therefore a potentially decreased likelihood of benefiting from cisplatin.[1,10,13] This study was approved by the University of California San Diego Institutional Review Board. Five independent users with various training backgrounds used the online tool to evaluate a cohort of 20 adult patients with nonmetastatic locally advanced or recurrent HNC and calculate output values for each model through medical record review. Before this evaluation, providers documented additional patient-reported comorbidity-specific questions (eg, self-rating of health, decreased socialization because of health) for retrospective evaluation and model input. Evaluators also completed a system usability scale (SUS) to assess the functionality of the online tool.[25]

Interrater reliability was evaluated by calculating the intraclass correlation coefficients (ICCs) for the CCI, ACE-27, CIRS-G, G8, CARG, and GCE models as ordinal or continuous variables.[26]

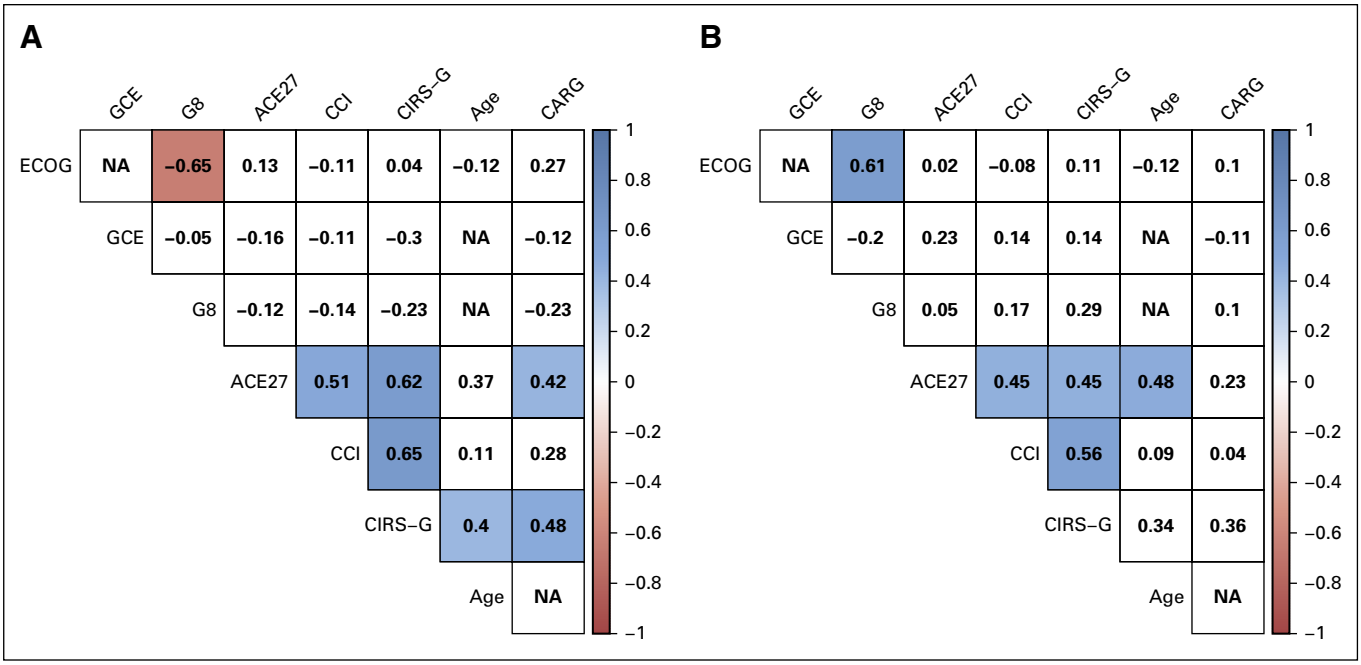

Fig 2. Correlation between the indices of comorbidity. (A) Correlation matrix showing correlation coefficients (ρ) between the CCI (Charlson Comorbidity Index), ACE-27 (Adult Comorbidity Evaluation-27), CIRS-G (Cumulative Illness Rating Scale for Geriatrics), G8 (Geriatric 8), CARG (Cancer and Aging Research Group), and GCE (Generalized Competing Event) models, age, and Eastern Cooperative Oncology Group (ECOG) performance status, with model outputs as continuous or ordinal variables or (B) binary outputs representing moderate to severe comorbidity. Colored panels indicate statistically significant ($P < .01$) correlation with the Spearman rank test. NA indicates that correlation was not assessed because of overlapping data inputs.

Fleiss' kappa test was calculated to determine whether raters agreed that the patient met a binary threshold level of comorbidity for each model. Values for ICCs and Fleiss' kappa range between 0 and 1, with 0.6 to 0.74 indicating good and 0.75 to 1.0 indicating excellent levels of interrater agreement, respectively.[27] A Fleiss' kappa of 0.6 or greater was selected as an acceptable level of interrater agreement.

After validating interrater reliability, an additional 20 patients were retrospectively evaluated by a single user to assess correlation between comorbidity models. Correlations between comorbidity models, age, and ECOG PS were calculated for the cohort of 40 patients by using the Spearman rank test with $P < .01$ selected as statistically significant.[28] Correlations between age and the GCE, G8, and CIRS-G models and between ECOG PS and the GCE model were not assessed because they contained overlapping input variables. Data were analyzed in R version 3.4.3 (www.r-project.org).

RESULTS

The evaluated cohort of 40 patients included adult patients with American Joint Committee on Cancer, 7th edition (AJCC 7) stages III and IV and recurrent HNC (Table 2). Of note, the GCE model was not developed to evaluate patients with nasopharynx, para-nasal sinus, or recurrent HNC. Evaluators included three radiation oncology residents (post-graduate years 2 to 5), a clinical trial coordinator specializing in HNC, and a clinical research associate. No additional training was given aside from instruction provided on the Web site. The mean user rating for the tool from the SUS questionnaire was 87.7 of 100, indicating a high degree of usability. ICC values were 0.74 (95% CI, 0.58 to 0.87) for the CCI, 0.68 (95% CI, 0.50 to 0.83) for the ACE-27, 0.62 (95% CI, 0.43 to 0.79) for the CIRS-G, 0.86 (95% CI, 0.76 to 0.93) for the G8, 0.71 (95% CI, 0.54 to 0.85) for the CARG, and 0.93 (95% CI, 0.87 to 0.97) for the GCE models (Fig 1A). Fleiss' kappa values were 0.67 for the CCI, 0.60 for the ACE-27, 0.60 for the CIRS-G, 0.85 for the G8, 0.67 for the CARG, and 0.93 for the GCE models (Fig 1B). The G8 and GCE models were found to have excellent agreement between evaluators on both the ICC and Fleiss' kappa tests. The CCI, ACE-27, CIRS-G, and CARG models were found to have a good level of agreement between evaluators.

The CIRS-G and ACE-27 models had the lowest agreement between evaluators. These indices had the highest number of inputs (14 and 27, respectively) and required evaluators to rate various diseases on a scale of severity. The GCE model had the highest agreement between evaluators. This model had the fewest number of inputs and required primarily objective data (eg, BMI, age, tumor stage).

Multiple sources of interrater discrepancy were identified. Evaluators differed significantly when they were required to rate the severity of comorbidities (eg, the CIRS-G and ACE-27 models). When identifying comorbidities, evaluators differed on whether they assigned a new diagnosis to a patient on the basis of laboratory or vital signs (eg, anemia, hypertension) if they did not already have the diagnosis formally documented in the medical record. Answers to patient questions such as the ability to ambulate were documented by providers but often required some interpretation by evaluators, which introduced potential discrepancy between model outputs.

The ACE-27, CCI, and CIRS-G models are based on the presence and severity of concurrent illnesses. There was a statistically significant degree of correlation for model output and whether the patient was identified as having moderate to severe comorbidity between these indices (Fig 2). PS was not correlated with the CCI, ACE-27, CIRS-G, or CARG models but was correlated with lower G8 model outputs (lower G8 score indicates higher degree of frailty). Increased age was significantly correlated with a higher CIRS-G score ($\rho = 0.4$; $P < .01$). Increased age was also significantly correlated with increased score using the ACE-27 model ($\rho = 0.48$; $P < .01$).

In conclusion, evaluating comorbidity in patients with HNC is critical for determining survival prognosis and predicting the benefit of treatment intensification.[3,10,14,15] Several validated comorbidity prognostic tools have been developed for general use, including the CCI, ACE-27, CIRS-G, G8, and CARG indices. Furthermore, HNC-specific GCE models can be used to predict patients' relative probability of disease-specific mortality versus competing mortality. We developed an online tool that aggregates these models for clinical and research purposes with a high degree of usability as rated by users on the SUS questionnaire.

In this study, we found an excellent level of agreement between evaluators for the G8 and GCE models. The CCI, ACE-27, CIRS-G, and CARG models had a good level of agreement between evaluators. Our results show that these indices are reliable when evaluators of various backgrounds and levels of training use the online tool. The interrater reliability for the CCI and CARG were similar to previously reported values of 0.74 and 0.76, respectively.[15] In our study, indices that had a greater number of inputs and those that required grading severity of disease had lower interrater agreement. The GCE model had a high interrater agreement, requiring input of only objective patient and disease data; however, agreement was not perfect, suggesting that data entry itself may be a source of variability.

The ACE-27, CCI, and CIRS-G quantify a patient's burden of concurrent noncancer illness. Each model has been shown to be predictive of morbidity and mortality.[3,15] We found significant correlation between the ACE-27, CCI, and CIRS-G, which suggests that it is redundant to calculate each of these models for a given patient. Interestingly, however, PS graded on the ECOG scale was not statistically significantly correlated with any of the comorbidity models except for G8. The G8 is designed to evaluate frailty of elderly patients, with inputs including patient mobility and self-rating of health. The lack of correlation between PS and other comorbidity metrics has been previously described,[15,16] suggesting that PS is a poor surrogate for clinical comorbidity evaluation.

Increased age was correlated with a higher CIRS-G score and with moderate to severe comorbidity using the ACE-27 model. These findings suggest that comorbidity is only moderately correlated with age and should be separately evaluated as a covariate in elderly patients. Age was an explanatory variable in the GCE, G8, and CARG models, so we did not test age correlations for these measures. Our study establishes that the previously validated CCI, ACE-27, CIRS-G, G8, CARG, and GCE models can be easily implemented clinically using an online tool with high interrater agreement. Most indices were independent of ECOG PS score, indicating that PS alone is not a sufficient indicator of comorbidity.

Calculating all indices for patients is likely to be too burdensome for routine clinical practice. Selection of an index or indices for clinical decision making should be based on the intended utility of the model. The ACE-27, CCI, and CIRS-G models are similarly designed to quantify cumulative comorbidity and are highly correlative. The G8 model measures patient frailty and correlates with ECOG PS. The CARG model is designed to predict the risk of moderate to severe chemotherapy toxicity in elderly patients.

GCE modeling is unique in that it predicts the patient's relative cancer versus noncancer risk, which can determine the benefit of more aggressive treatment. Additional research is needed to compare the ability of these comorbidity models to predict mortality and treatment morbidity in patients with HNC.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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