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Comparison of Scoring Methods for ACE-27: Simpler Is Better

Dorina Kallogjeri, MD, MPH^a, Jay F. Piccirillo, MD^a, Edward L. Spitznagel Jr., PhD^b, and Ewout W. Steyerberg, PhD^c

^aClinical Outcomes Research Office, Department of Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, St. Louis, Missouri, USA ^bDepartment of Mathematics, Washington University, St. Louis, Missouri, USA ^cDepartment of Public Health, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands

Abstract

Objective—To examine the prognostic value of different comorbidity coding schemes for predicting survival of newly diagnosed elderly cancer patients.

Materials and Methods—We analyzed data from 8,867 patients aged 65 years of age or older, newly diagnosed with cancer. Comorbidities present at the time of diagnosis were collected using the Adult Comorbidity Evaluation-27 index (ACE-27). We examined multiple scoring schemes based on the individual comorbidity ailments, and their severity rating. Harrell's c index and Akaike Information Criterion (AIC) were used to evaluate the performance of the different comorbidity models.

Results—Comorbidity led to an increase in c index from 0.771 for the base model to 0.782 for a model that included indicator variables for every ailment. The prognostic value was however much higher for prostate and breast cancer patients. A simple model which considered linear scores from 0 to 3 per ailment, controlling for cancer type, was optimal according to AIC.

Conclusion—The presence of comorbidity impacts on the survival of elderly cancer patients, especially for less lethal cancers, such as prostate and breast cancers. Different ailments have different impacts on survival, necessitating the use of different weights per ailment in a simple summary score of the ACE-27.

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Corresponding Author: Jay F. Piccirillo, MD, Clinical Outcomes Research Office, Department of Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, Campus Box 8115, 660 South Euclid Avenue, St. Louis, MO, USA 63110, Tel: 001-314-362-6841, Fax: 001-314-362-7522, piccirilloj@ent.wustl.edu.

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Author Contributions

Dr. Kallogjeri contributed to the conception and design of the manuscript, data collection, analysis and interpretation of data, and manuscript writing.

Dr. Piccirillo contributed to the conception and design of the manuscript, data collection, analysis and interpretation of data, and manuscript writing.

Prof. Spitznagel contributed to the conception and design of the manuscript, analysis and interpretation of data, and manuscript writing.

Prof. Steyerberg contributed to the conception and design of the manuscript, analysis and interpretation of data, and manuscript writing.

All authors provided final approval of the manuscript.

Disclosure Statement

The other authors have no conflict of interest to disclose.

Keywords

Comorbidity; comorbid ailment; elderly; cancer patients; prognostic; survival

INTRODUCTION

Elderly cancer patients often have other diseases, illnesses, and conditions at the time of their diagnosis. These diseases, illnesses, and conditions are referred to as comorbidities. Comorbidity is an independent predictor of survival and is important to the care of cancer patients. Patients with comorbidities have worse outcomes than patients with no such conditions.[1] Read et al.[2] demonstrated that the prognostic value of overall comorbidity is relative to the mortality burden of the index cancer. That is, comorbidity is prognostically most important in situations where the prognostic impact of the tumor is small.

The incidence of a new cancer diagnosis in the elderly population is reported as 25% between the ages of 65 and 74, 22% between the ages of 75 and 84, and 8% for individuals aged 85 and older.[3] Elderly patients tend to suffer from cancers that are not rapidly fatal, such as prostate, colon, uterus, and breast.[4–6] Elderly cancer patients also have more comorbid conditions and poorer physical and mental health than elderly peers with no cancer.[7;8] The presence and severity of some comorbidities increase with age, while other comorbidities decrease.[9] For instance, the prevalence and severity of dementia and congestive heart failure increased with age while HIV/AIDS and obesity decreased.

There are several comorbidity instruments and different methods of combining the prognostic impact of multiple diseases, illnesses, and conditions to create an overall score. [10] Some instruments require a detailed chart-based review, while others can be implemented with ICD-9 data contained within a hospital patient's discharge summary. Independent of the measurement method, comorbidities have been significantly associated with outcomes in mortality and quality of life of elderly cancer patients.[11]

Acknowledging the importance of comorbidities, different groups have focused their efforts on comparing the different methods of assessing comorbidities with the goal of identifying a better assessment tool as relates to elderly cancer patients.[12] Piccirillo et al[1] modified the original Kaplan-Feinstein Index (KFI)[13] by adding several health conditions (e.g., diabetes, HIV/AIDS, dementia) not present on the original KFI, and created a comorbidity index for newly diagnosed cancer patients [1]. The new index is called the Adult Comorbidity Evaluation-27 (ACE-27) index. The ACE-27 is a validated instrument that captures cogent comorbidities for cancer patients and grades severity of the ailments at the time of cancer diagnosis.[14; 15]

Using modern methods of analysis, we revisited the issue of quantifying comorbidity accurately in elderly cancer patients to appropriately reflect prognosis. The goal of our study was to examine the impact of different comorbidity scoring schemes for newly diagnosed elderly cancer patients.

MATERIALS AND METHODS

Study population

The study population consisted of 9,253 patients aged 65 years or older, diagnosed with cancer between 2000 and 2007 at Barnes Jewish Hospital in Saint Louis (BJH), for whom detailed comorbidity data was collected using ACE-27[14] index. Comorbid health information was collected for each patient by cancer registrars trained to use the ACE-27

method as part of an on-going cancer education program sponsored by the National Cancer Institute.[15] Data elements, such as date of diagnosis, demographic information, cancer diagnosis, Surveillance, Epidemiology, and End Results (SEER) tumor staging, and survival, were collected as part of the cancer registrars' routine job. The presence of one or more different comorbid ailments, present at time of cancer diagnosis, was coded for all patients using ACE-27. Of the 9,253 patients, information on race, gender, tumor staging, or survival was missing for 386 (4%) patients and these patients were thus excluded from analysis. The "zero-time" for the study was defined as the date of cancer diagnosis and the duration to the last follow-up was cited relative to this zero-time. The date of last follow-up was July 2010.

Classification of data

Patients were classified into one of three race categories: white, black, or other. Cancer diagnosis was recorded by cancer registrars based on the pathology report documenting the malignancy. The dataset included malignancies of the following body systems: lung, breast, prostate, colorectal, digestive, genitourinary, head and neck, gynecologic, skin (excluding basal cell), musculoskeletal, or other. Under the "other" category we included malignancies of the nervous, lymphatic, ophthalmologic, blood, other male genitalia systems together with mesotheliomas and thyroid tumors. The SEER stage uses clinical and pathological information in the chart, and categorizes tumors by the method of spread. SEER Summary Stage is a required data field for cancer registrars. Prior to data analysis, SEER summary staging was re-categorized into one of three main groups: in situ/local, regional, or distant.

Comorbid ailments and coding

Concomitant medical conditions, not related to the index cancer, were captured by cancer registrars through medical chart review using the ACE-27. The cogent comorbid conditions were grouped under each of the following systems: cardiovascular, respiratory, gastrointestinal, renal, endocrine, neurological, psychiatric, rheumatologic, immunological, malignancy prior to index malignancy or concomitant malignancy with index malignancy, substance abuse, and obesity. Cogent individual comorbid ailments, except for obesity, were classified according to the severity of organ decompensation into one of three severity categories: none, mild, moderate, or severe. Morbid obesity defined as BMI greater than or equal to 38, was scored as moderate. The ACE-27 form and related material is available on line at: <http://oto2.wustl.edu/clinepi/comorbid.html>

Comorbidity scoring schemes

Multiple comorbidity scoring schemes were examined based on the individual comorbidity ailments and their severity ratings. The characteristics of the eight different comorbidity scoring schemes and their relationship to each other are described in greater detail below and are presented in Table 3.

A1 and A2: Kaplan-Feinstein Score—The overall comorbidity severity score is defined according to the scoring algorithm for the original Kaplan-Feinstein Index.[(13)] In that scoring system, the possible overall scores are none (0), mild (1), moderate (2), or severe (3). The overall comorbidity score for an individual patient represents the severity grade of organ decompensation for the highest-ranked single comorbid ailment or, in the case in which there are two comorbid ailments in 2 different organ systems each rated as moderate organ decompensation, the overall score is severe. This comorbidity scoring scheme is currently the recommended scoring algorithm for the ACE-27. The overall ACE-27 score also ranges from none (0) to severe (3). This score is considered as a linear

term (labeled as A1 in Table 3) with 1 degree of freedom (df), as well as a categorized version (labeled as A2) with 3df.

B1: Simple Sum—The simplest extension of the Kaplan-Feinstein Index score is to allow the maximum score to reflect the sum of each individual comorbid condition rather than restrain the maximum score to 3. Similar to the Kaplan-Feinstein Index score, the simple sum does not allow for nonlinearity, and assumes each comorbidity condition to have identical weights. The simple score based on this scheme (labeled as B1 in Table 3) ranges theoretically from 0 in the case of no comorbidity present, to 77 ($= 25 \times 3 + 2$) in the cases of the highest severity score recorded on every single ailment.

C1, C2, C3: Individual Comorbidity Scores—A further extension of the coding scheme is to allow for different weights for each comorbid ailment. Scheme C1 considers the scores ranging from 0 to 3 per ailment. Scheme C2 dichotomizes each individual ailment, with comorbidity severity none (Grade 0) or mild (Grade 1) grouped together reflecting minor comorbidity and comorbidity severity groups moderate (2) and severe (3) grouped to reflect major comorbidity. Scheme C3 considers categorized scores per condition, with three indicator variables generated for every ailment, except obesity. For obesity, only one indicator variable was possible, namely, moderate vs. none.

D1, D2: Non-Linear Weighting—For non-linear weighting, three different scoring variables were used: *G1*, *G2*, and *G3* to allow for non-linearity in the scores from 0 to 3 per condition. *G1* is the sum of all comorbid ailments scored as mild in their severity, *G2* is the sum of all moderate severity ailments, and *G3* is the sum of all severe coded ailments. The first scoring scheme (D1) uses just *G1*, *G2*, and *G3* with the purpose of non-linear weighting and equal weights for each comorbidity (3df). To create the second non-linear weighting scheme (D2), the individual comorbid scores were added to scheme D1 to create a new scheme which allowed for different weights per condition (29df).

Analytical Work—The base model included the age-group (5 categories), race (3 categories), gender (2 categories), cancer site (11 categories), and SEER stage (4 categories). All comorbidity schemes were considered in addition to this base model. Models were compared across all cancer sites and within the 4 most common cancer sites (lung, prostate, colorectal, and breast). The Cox proportional hazard model was used for univariate and multivariable analyses. The likelihood ratio chi-square statistic, Akaike Information Criterion (AIC), Nagelkerke's *R*-square, and Harrell's *c* index were used to evaluate the performance of the different comorbidity models. The AIC is a version of chi-square that is penalized by the number of independent variables in the model, thus allowing comparison of models of varying complexity.[16] AIC By Comorbidity is calculated as model *chi-square minus 2*df*, where model *chi-square* is the difference in -2 log likelihood of a model with and without the specific comorbidity scoring, and *df* is the degrees of freedom used by adding the specific comorbidity scoring. AIC By Comorbidity is the magnitude of reduction (absolute value) of the AIC for each model as compared to the baseline model without comorbidity. The larger the value of AIC By Comorbidity, the better the model performance is. AIC hence penalizes more complex models, similar to measures such as the Bayesian Information Criterion (BIC).[17] The *c* index is defined as the proportion of all usable patient pairs in which the predictions and outcomes are concordant. [18] For binary outcomes, *c* is identical to the area under the receiver operating characteristic curve. All presented *c* statistics were corrected for optimism through a bootstrapping procedure using 200 bootstrap samples, drawn with replacement from the original samples.[17] The mean decrease in *c*-index resulting from bootstrapping was

negligible ($p=0.001$). We used SAS® version 9.2., STATA-SE version 10, R version 2.11.1. This study was approved by Washington University Human Research Protection Office.

RESULTS

Patient characteristics

The characteristics of 8,867 elderly patients (65 years of age or older at the time of cancer diagnosis) diagnosed with cancer at BJH are described in Table 1. Of the total 8,867 patients, 82% were between 65 and 79 years old at the time of cancer diagnosis, and 53% were males. The sample consisted of 83% Caucasians, 16% African-Americans, and 1% other races. The frequency distribution of the Kaplan-Feinstein Index overall comorbidity score was none 1,660 (19%), mild 3,705 (42%), moderate 1,960 (22%) and severe 1,542 (17%).

The most frequent cancer site reported was the lung (1,447, 16%), followed by prostate (1,293, 15%), digestive system (1,203, 14%), colorectal (910, 10%), and breast (783, 9%). The SEER tumor staging was distributed as follows: in situ and local (4,150, 47%), regional (2,502, 28%), and distant (2,215, 25%).

Outcome

Patient overall survival was the outcome of interest. At the time of last follow-up, 3,943 (44.5%) of the patients were alive and 4,924 (55.5%) were dead. The median follow-up time was 30 months and inter-quartile range was 10 to 61 months. The median overall survival was 44.9 months.

Bivariate analyses

Univariate Cox proportional hazards models were run with each of the main characteristics included in the base model and the hazard ratios generated are reported in Table 1. A steady increase in hazard ratio (HR) was noticed with every 5-year increase in age. There was no significant difference in survival for females compared to males. African-Americans were 1.27 [1.18 to 1.36] times more likely to die than Caucasians. As the morphological stage of the tumor increased, so did the mortality risk - when compared to patients with in situ/local tumors, patients with regional tumors had a HR of 2.50 [2.32 to 2.68], and 5.89 [5.49 to 6.32] for distant spread of tumor.

The hazard ratio was markedly different for tumors from different sites. When patients with specific types of cancers were compared to the rest of the study population, lung, digestive, musculoskeletal, and other rare cancers grouped together had an increased risk for mortality. For example, lung cancer patients had a HR of 2.48 [2.32 to 2.64] relative to all other patients; patients with digestive system cancer had a HR of 2.87 [2.68 to 3.08] and patients with less prevalent cancers grouped under the "other" category had a HR of 1.55 [1.43 to 1.68].

As severity of overall comorbidity, calculated based on Kaplan-Feinstein Index algorithm, increased so did the mortality risk. When compared to patients with no comorbidities, patients with mild comorbidity had a HR of 1.43 [1.31 to 1.56], moderate 1.85 [1.68 to 2.03], and severe 2.05 [1.86 to 2.26]

Multivariable analysis

We performed a Cox regression analysis of the complete dataset with all the cancer sites included, followed by separate analyses for subsets of data for each of the following cancer sites: breast, prostate, colorectal, and lung. Table 2 summarizes the impact of each of the

comorbid conditions included in ACE-27 in prediction of overall survival after controlling for age group, gender, race, tumor stage, and tumor site (for the all cases model). Based on the likelihood ratio test, with the reported degrees of freedom, the base model (age group, gender, race, diagnosis, and SEER stage) and all comorbidity models were highly statistically significant (i.e., p values all less than 0.001). The interactions of comorbidity by type of cancer were statistically significant.

Discriminatory power of the created models was determined using Harrell's *c*-index generated from STATA's 'estat concordance' procedure. Overall, all our models, including the models containing all cases and the four models containing cancer-specific patients, were able to discriminate between high- and low-risk patients with *c*-indices ranging from 0.71 to 0.81. In the baseline model, without comorbidity, the *c*-index was 0.772, AIC was 79997.842 and Nagelkerke's R square was 38.8%. In all cases, the models containing comorbidity performed better than the baseline model, which did not contain comorbidity. The best discriminating power for "All Cases" was observed in Model C3 (*c*=0.782), which showed an improvement of 0.010 over the model with no comorbidities (*c*=0.772) (Table 3). Model C3 was also best in all cancer-specific models (Breast *c*=0.796; Prostate *c*=0.808; Colorectal *c*=0.769; Lung *c*= 0.712) with improvements of 0.050, 0.086, 0.058, and 0.015 respectively over the model with no comorbidities for each site with *c*-indexes 0.745, 0.723, 0.711 and 0.697 (Table 4). The discriminating power of Model C3 was followed by Models C1 and D2.

Model C3 was also the model with the greatest number of terms with 71 degrees of freedom more than the model with no comorbidities (df =19). However, there were models with smaller numbers of terms that had essentially the same predictive power as Model C3. For instance, based on the AIC criterion, Model C1 is the best for "All Cases", "Breast", and "Prostate" with a reduction in AIC as compared to the baseline model of 283, 34, and 85, respectively. Model D2 was the best for colorectal (delta AIC=52) and Model B1 was the best for lung (delta AIC=22).

Comparison of performance between models was assessed by the difference in Nagelkerke's R square statistic calculated for each of the Cox proportional hazard models versus the model with no comorbidities. As shown in Table 3, Model C3 was again the best performer with an improvement in R square of 2.8% over the base model (R²=0.388), followed by Model D2 (2.3%) and Model C1 (2.3%) for all cases included, as well as for each of the specific sites. It should be noted, however, that Nagelkerke's R square calculation does not adjust for the number of terms in the model.

DISCUSSION

This study showed the importance and the need for assessing the weight of different comorbid ailments and their severity. Overall, all the models containing comorbidity performed better than the baseline model, which did not contain comorbidity. The best comorbidity scoring method was in Model C1 where the degree of organ decompensation for each individual comorbid ailment was scored as 0=None, 1=Mild, 2=Moderate, or 3=Severe. The accuracy of the models did not increase as the complexity of the models increased. Furthermore, given the observed differential impact of comorbid ailments across different cancer types, it is best to develop weights for the different comorbid ailments within each cancer type. Interestingly, the model with the best AIC value for Lung (Model B1) different from the best model (Model C1) for all cases, breast, colorectal, and prostate. Lung cancer is a very aggressive type of cancer and comorbidities do not carry as much prediction of overall survival as they do for more latent cancers.

All of the models presented in this study were created by using different combinations and scoring algorithms of the comorbid elements included in the ACE-27 index. Each comorbid condition included in the ACE-27 index was chosen based on statistical and clinical significance.[14;19] The ACE-27 index includes serious comorbidities reported as frequent conditions among cancer patients and especially among those over 60 years of age.[20] While there are many studies that focus on comparing the prognostic accomplishments of different adaptations of the Charlson's scoring algorithm,[12;21–24] there are few studies that investigate such comparisons or evaluations using the ACE-27 index. Fang et al. reported that the chart-based ACE-27 and Charlson's comorbidity index differed in the distribution of patients, at baseline, according to levels of comorbidity severity.[25]

This study's analytical approach, using the Cox proportional hazard model, was performed on a large sample of cancer patients diagnosed and/or treated at Barnes Jewish Hospital/ Siteman Cancer Center, a comprehensive cancer center. A standard baseline model that included baseline demographic and tumor-specific characteristics, served as the starting point and the reference for comparisons. Acknowledging that the Kaplan-Feinstein scoring of the Adult Comorbidity Evaluation-27 index did not make maximal use of our data, we did not limit ourselves to just simple variation of the overall Kaplan-Feinstein score. Instead different calculation scores and schemes that went beyond the assumption of linearity were tested as well. Since models were distinguished by addition of different comorbidity calculations over the base model, differences in statistical performance and the level of improvement of the models were due to inclusion of this comorbidity calculation. All comparisons were made using the same set of patients. The sample size was more than 10 times as large as the number of variables included in our models, which protects against the possibility of over-fitting the data.[18] The comparison of our models was based on more than one criterion. The discriminate power of each model was assessed using Harrell's *c*-index. The *c*-index improvement in our models ranged from 0.010 to 0.086. In a logistic regression model, an improvement of 0.010 in the *c*-index would be associated with an improvement in classification of approximately 0.85% of the patients, and an improvement of 0.086 in the *c*-index would be associated with an improvement in the classification of approximately 7.3% of patients.

In addition, we also used Nagelkerke's R square and the AIC-index, which penalizes for the number of variables included in the model, in order to have a fair comparison of models with different levels of complexity.

This study has some limitations. Our study population includes only elderly patients with cancer. It is known that the prevalence of different comorbid conditions varies across the age spectrum.[9] Elderly patients suffer from more comorbid conditions than younger patients, and the incidence of more indolent cancers is higher in the elderly compared to the general population.[4–6;11;26;27] This may limit the generalizability or external validity of the results. Nevertheless, we feel the internal validity of the data is accurate for the following reasons: comorbid health information is routinely collected prospectively by trained cancer and thorough follow-up of all patients is performed regardless of type of cancer or number of comorbid ailments.

The number of comorbid ailments included in a comorbidity index will impact on the prognostic capabilities of the index. For example, Stukenborg et al.[28] reported in 2001 that the Elixhauser[29] comorbidity model provided better discrimination than the Deyo adaption of the Charlson index.[30] Although the dataset used for comparison was the same, and both methods were adjustments of the Charlson index, the number of comorbidities captured by the Elixhauser method was nearly twice the number of comorbidities captured by the Deyo method. In contrast, our comparisons are based on the same number of

comorbid ailments and try to identify better weighting of these conditions to increase the predictive power. Wang et al.[31] used a time-dependent comorbidity factor and assessed this factor in addition to baseline comorbidity to conclude that longitudinal assessment of comorbidity is an important predictor of survival. Their study also found that the best model combined both time-independent baseline comorbidity and the time-dependent comorbidity assessments. The worst fitting model included baseline comorbidity only. Overall the best fit models used the “the rolling” comorbidity measures that assumed chronic conditions persisted rather than measures using only prior years recorded diagnoses. Our study was limited in using only the time-independent baseline comorbidity, but one can argue on our approach’s support since the change in comorbidities after the cancer diagnosis can be a complication of the cancer or its treatment.[32]

A simple model (C1), which uses severity grading for each ACE-27 comorbid ailment, captures sufficient information to provide valid prognostic predictions. Model C1 is simpler than the original Kaplan-Feinstein scheme of scoring ACE-27. The accuracy of scoring did not improve substantially with models more complex than Model C1.

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Table 1

Descriptive Characteristics of 8,867 Patients Diagnosed With Cancer (2000–2007) at BJH with Comorbidities Assessed Using A Chart-Based Method (ACE-27)

	N	%	Hazard Ratio (HR)	95% Hazard Ratio Confidence Limits
Age groups				
65–69	2930	33	Ref.	--
70–74	2390	27	1.31	1.21 to 1.41
75–79	1920	22	1.58	1.46 to 1.71
80–84	1100	12	1.85	1.69 to 2.03
85	527	6	2.66	2.39 to 2.97
Gender				
Female	4202	47	Ref.	--
Male	4665	53	0.95	0.89 to 0.99
Race				
Caucasian	7394	83	Ref.	--
African-American	1366	16	1.27	1.18 to 1.36
Other	107	1	0.86	0.64 to 1.15
Comorbidity Score *				
None	1660	19	Ref.	--
Mild	3705	42	1.43	1.31 to 1.56
Moderate	1960	22	1.85	1.68 to 2.03
Severe	1542	17	2.05	1.86 to 2.26
SEER Tumor staging				
In Situ/Local	4150	47	Ref.	--
Regional	2502	28	2.50	2.32 to 2.68
Distant	2215	25	5.89	5.49 to 6.32
Main cancer diagnosis **				
Lung	1447	16	2.48	2.32 to 2.64
Breast	783	9	0.31	0.27 to 0.36
Prostate	1293	15	0.19	0.17 to 0.22
Colorectal	910	10	0.83	0.75 to 0.91
Digestive	1203	14	2.87	2.68 to 3.08
Urinary	732	8	0.81	0.73 to 0.90
Head and neck	436	5	0.93	0.81 to 1.06
Gynecological	771	8	0.91	0.82 to 1.01
Skin	184	2	0.64	0.51 to 0.80
Musculoskeletal	163	2	1.12	0.92 to 1.37
Other	945	11	1.55	1.43 to 1.68

* Calculated based on original Kaplan-Feinstein scoring method.

** The reported survival HR for each site is relative to all the others together (e.g. lung cancer vs. non-lung cancer)

Table 2

Comparison of Adjusted Hazard Ratios (HR) for the 26 Comorbid Ailments Included in the Adult Comorbidity Evaluation-27 Index Generated from Model C1

Comorbidity Ailment	All cases			Breast Cancer			Prostate Cancer			Colorectal Cancer			Lung Cancer		
	HR	95% HR Confidence Limits		HR	95% HR Confidence Limits		HR	95% HR Confidence Limits		HR	95% HR Confidence Limits		HR	95% HR Confidence Limits	
MI	1.02	0.97	1.08	0.83	0.58	1.20	1.22	0.96	1.56	1.12	0.96	1.31	0.98	0.89	1.08
Angina	1.06	0.99	1.13	1.24	0.78	1.99	1.11	0.83	1.49	1.02	0.84	1.25	1.14	0.99	1.32
CHF	1.21	1.12	1.31	0.85	0.61	1.19	1.44	0.99	2.08	1.63	1.33	2.00	1.08	0.91	1.27
Arrhythmias	1.07	1.02	1.12	1.49	1.16	1.92	1.57	1.29	1.91	1.06	0.91	1.22	1.05	0.96	1.15
HTN	0.99	0.94	1.05	0.82	0.60	1.12	1.00	0.75	1.34	0.96	0.79	1.17	0.96	0.85	1.08
Venous	1.01	0.97	1.05	0.84	0.66	1.07	0.98	0.79	1.22	1.09	0.97	1.23	1.01	0.92	1.10
Arterial	1.09	1.01	1.18	1.27	0.58	2.77	1.62	1.02	2.59	1.00	0.76	1.31	1.14	1.00	1.30
Respiratory	1.18	1.12	1.24	1.72	1.33	2.21	1.59	1.22	2.08	1.13	0.94	1.36	1.13	1.05	1.21
Hepatic	1.41	1.25	1.60	1.06	0.13	8.48	9.62	2.28	40.60	1.38	0.50	3.79	1.28	0.92	1.78
Stomach	0.97	0.88	1.07	1.00	0.45	2.27	0.42	0.17	1.05	0.86	0.61	1.21	0.90	0.73	1.12
Pancreas	1.47	1.08	2.00	.	.	.	18.57	2.60	132.89	.	.	.	1.16	0.61	2.20
Renal	1.33	1.21	1.45	3.09	2.05	4.66	2.35	1.51	3.65	1.77	1.30	2.41	1.13	0.93	1.38
Diabetes	1.13	1.08	1.18	1.31	1.01	1.71	1.49	1.14	1.96	1.21	1.05	1.40	1.09	0.98	1.21
Stroke	1.09	1.01	1.18	1.00	0.73	1.36	0.88	0.60	1.29	1.15	0.90	1.47	1.05	0.90	1.22
Dementia	1.57	1.38	1.78	2.39	1.54	3.70	1.65	0.67	4.06	1.64	1.23	2.18	1.43	1.04	1.96
Paralysis	1.15	0.72	1.83	.	.	.	.	.	.	2.33	1.20	4.55	0.93	0.48	1.80
Neuromuscular	1.28	1.07	1.54	1.91	1.08	3.38	16.52	3.04	89.64	1.31	0.74	2.32	1.17	0.73	1.88
Psychiatric	1.13	1.01	1.26	1.24	0.70	2.21	0.73	0.31	1.73	1.41	1.04	1.91	1.17	0.92	1.48
Rheumatologic	1.15	1.01	1.30	1.57	0.74	3.34	1.88	0.85	4.16	1.09	0.60	1.96	1.24	0.99	1.55
AIDS	1.76	0.83	3.70	.	.	.	.	.	.	.	.	.	.	.	.
Solid tumor	1.07	1.03	1.11	1.03	0.86	1.23	1.72	1.49	1.98	1.08	0.97	1.20	0.98	0.90	1.06
Leukemia	1.47	1.21	1.80	2.49	0.84	7.40	0.00	0.00	.	3.21	1.74	5.92	1.09	0.60	1.97
Lymphoma	1.09	0.88	1.35	2.39	1.36	4.20	2.60	0.95	7.14	1.27	0.56	2.88	1.05	0.80	1.39
Alcohol	1.19	1.02	1.38	0.00	0.00	--	2.88	1.35	6.12	0.64	0.27	1.51	0.93	0.72	1.21

	All cases		Breast Cancer		Prostate Cancer		Colorectal Cancer		Lung Cancer	
	HR	95% HR Confidence Limits	HR	95% HR Confidence Limits	HR	95% HR Confidence Limits	HR	95% HR Confidence Limits	HR	95% HR Confidence Limits
Comorbidity Ailment										
Drugs	2.16	1.44 3.25	.	.	.	.	3.07	1.56 6.02	1.57	0.88 2.80
Obesity	1.06	0.95 1.19	0.89	0.49 1.60	0.08	0.00 1.91	1.11	0.84 1.48	1.11	0.82 1.51

Table 3

Comparison of Harrell's c concordance statistic, AIC and Nagelkerke's R square resulting from Cox-proportional hazard model analysis of models including different comorbidity coding schemes versus the model with no comorbidities.

Comorbidity System	Definition	Allows for non-linearity?	Different Weights?	Model Label	Delta [*] c-index [§]	AIC [€] by comorbidity	Delta R square [¥] (%)
Kaplan-Feinstein	Highest-ranked ailment, or 2 Grade 2 ailments equals Severe (Grade 3)	No	No	A1	1	105	0.8
		Yes	No	A2	3	103	0.8
Simple Sum	Sum of scores	No	No	B1	1	189	1.3
Individual Comorbidity Scores	Different weight for each comorbid ailment	No	Yes	C1	26	283	2.3
		NA	Yes	C2	26	178	1.6
		Yes	Yes	C3	71	267	2.8
Non-Linear Weighting	Prognostic weights per grade of comorbidity	Yes	No	D1	3	186	1.3
		Yes	Yes	D2	28	280	2.3

^{*} Delta refers to change in performance of comorbidity plus the baseline model to the baseline model alone.

[§] Delta c-index is the increase in the c-index for each model as compared to the baseline model with c-index=0.772. The larger the value, the better the model discrimination is.

[€] AIC by comorbidity is the magnitude of reduction (absolute value) of the AIC for each model as compared to the baseline model with AIC=79997.842. This is attributable only to comorbidity inclusion in the model. The larger the value of AIC by comorbidity, the larger the reduction in AIC is, and the better the model performance.

[¥] Delta R Square is the magnitude of change of Nagelkerke's R square from each model relative to the baseline model with R square=38.8%. The larger the value of delta R square, the larger the improvement in the model's performance in explaining the variability of outcome.

Table 4

Comparison of Harrell's c concordance statistic, AIC and Nagelkerke's R square resulting from Cox-proportional hazard model analysis of models including different comorbidity coding schemes versus the model with no comorbidities per each of the four main cancer sites.

Model	Delta df	Delta c-index	AIC by comorbidity	Delta R square (%)
Breast Cancer (n=1651) *	NA	0.745	2363	18.5
A1	1	0.009	3	0.5
A2	3	0.012	1	0.7
B1	1	0.019	15	1.7
C1	22	0.043	34	7.8
C2	20	0.040	34	7.4
C3	51	0.050	12	11.1
D1	3	0.019	12	1.8
D2	24	0.042	31	7.9
Prostate Cancer (n=2514) *	NA	0.723	2943	14.4
A1	1	0.044	29	2.1
A2	3	0.047	26	2.1
B1	1	0.060	57	3.8
C1	23	0.083	85	8.3
C2	20	0.077	44	5.4
C3	53	0.086	60	10.4
D1	3	0.057	56	4.0
D2	25	0.081	85	8.5
Colorectal Cancer (n=1699) *	NA	0.711	5701	25.8
A1	1	0.017	22	1.9
A2	3	0.017	18	1.9
B1	1	0.026	42	3.5
C1	24	0.048	51	7.7
C2	23	0.038	44	7.0
C3	58	0.058	47	12.2
D1	3	0.026	42	3.8
D2	26	0.041	52	8.0
Lung Cancer (n=2538) *	NA	0.697	15024	27.7
A1	1	0.004	16	0.9
A2	3	0.005	14	1.0
B1	1	0.006	22	1.2
C1	25	0.010	2	2.6
C2	25	0.007	-11	1.9
C3	64	0.015	-27	4.9

Model	Delta df	Delta c-index	AIC by comorbidity	Delta R square (%)
D1	3	0.006	19	1.3
D2	27	0.010	-1	2.6

* The row with the label of the cancer site reports the respective values of the baseline model for each cancer site.

§ Delta c-index is the magnitude of increase in c-index for each model as compared to the baseline model. The larger the value, the better the model discrimination is.

€ AIC by comorbidity is the magnitude of reduction (absolute value) of the AIC for each model as compared to the baseline model. This is attributable only to comorbidity inclusion in the model. The larger the value of AIC by comorbidity, the larger the reduction in AIC is and the better the model performance.

¥ Delta R Square is the magnitude of change of Nagelkerke's R square from each model to the baseline model with. The larger the value of delta R square, the larger the improvement in the models performance in explaining the variability of outcome.