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VALIDATION OF A COMBINED COMORBIDITY INDEX

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Abstract—The basic objective of this paper is to evaluate an age–comorbidity index in a cohort of patients who were originally enrolled in a prospective study to identify risk factors for peri-operative complications. Two-hundred and twenty-six patients were enrolled in the study. The participants were patients with hypertension or diabetes who underwent elective surgery between 1982 and 1985 and who survived to discharge. Two-hundred and eighteen patients survived until discharge. These patients were followed for at least five years post-operatively. The estimated relative risk of death for each comorbidity rank was 1.4 and for each decade of age was 1.4. When age and comorbidity were modelled as a combined age–comorbidity score, the estimated relative risk for each combined age–comorbidity unit was 1.45. Thus, the estimated relative risk of death from an increase of one in the comorbidity score proved approximately equal to that from an additional decade of age. The combined age–comorbidity score may be useful in some longitudinal studies to estimate relative risk of death from prognostic clinical covariates.

Comorbidity Prognosis

INTRODUCTION

The Charlson comorbidity index was originally designed to classify prognostic comorbidity in longitudinal studies [1]. It has been used in a number of studies to stratify patients in order to control for the confounding influence of co-morbid conditions on overall survival. In larger studies that involve more than 1 or 2 years of follow-up, both age and comorbidity predict the probability of death from comorbid disease. In our initial paper [1], we proposed that for some studies it might be useful to create a combined age–comorbidity index using a method proposed by Hutchinson *et al.* [2]. In short, the relative risks obtained from the proportional hazards model have been used to create a single prognostic variable indicative of subsequent risk. In this instance, the risk from age and the risk from comorbid disease have been combined into a single variable estimating the risk of death. When such a combined age–comorbidity variable was originally proposed, it was noted that validation in a separate cohort would be required.

The purpose of this paper is to validate the prognostic accuracy of the proposed age–comorbidity index in a separate cohort. The index was previously proposed in a separate report on a different cohort [1].

METHODS

Assembly of population

A total of 226 patients were studied. To focus on the long term prognosis of the complications among patients who survived hospitalization

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and to avoid inflating the long term adverse effects of post-operative complications by including their short term impact, the 8 patients who died in hospital were eliminated from further consideration. Thus, there were 218 patients who survived to discharge; these patients are the subject of this paper.

Patients who had essential hypertension or diabetes and who were undergoing elective general surgery between July 1982 and September 1985 were eligible for enrollment in a study of risk factors for peri-operative complications. The enrolled patients were from the general surgical service and were scheduled to undergo elective non-cardiac surgery for diagnoses such as peripheral vascular disease and aortic aneurysm. The details of the screening procedure have been reported elsewhere [3]. The criteria for hypertension [3] were: (1) for patients <30 years, systolic blood pressure (BP) $\geqslant 150$ mmHg or diastolic BP $\geqslant 90$ mmHg; (2) for patients $\geqslant 30$ years, systolic BP $\geqslant 160$ mmHg or diastolic BP $\geqslant 95$ mmHg; or (3) treatment with any medication explicitly employed to reduce blood pressure. The criteria for diabetes were: (1) treatment with insulin or oral hypoglycemic agents; (2) elevated fasting glucose on more than one occasion (plasma $\geqslant 140$ mg/dl; whole blood $\geqslant 120$ mg/dl). The protocol was reviewed and approved by the Institutional Human Rights Committee. Informed consent was obtained from all patients.

Pre-operative evaluation

Pre-operatively, basic demographic and clinical data were recorded. The history of comorbid conditions, which included the disease for which the patient was undergoing surgery, was obtained using standardized questions and criteria. For example, angina was defined as definite or probable angina according to the Rose criteria [4]. Myocardial infarction included patients who had been hospitalized for chest pain and developed either new Q waves in at least 2 leads that were 0.04 seconds in duration and 1 mm in depth, new ST segment depression of 1 mm or more or new T wave inversion that persisted for 7 days, with elevation of creatinine kinase (CK) or CK–MB isoenzyme [5]. Congestive heart failure included patients with a definite history of pulmonary edema, paroxysmal nocturnal dyspnea, or dyspnea on exertion, not in the setting of an acute myocardial infarction, arrhythmia, or sepsis who responded to treatment and who required continued pharmacologic therapy.

The Charlson comorbidity score was calculated for each patient as the total of the patient's comorbid conditions which have been weighted. A higher Charlson comorbidity score indicates an increased severity of condition. Conditions with a weight of one included: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes. Conditions with a weight of two included: hemiplegia, moderate or severe renal disease, diabetes with end organ damage and any malignancy. Moderate or severe liver disease (e.g., cirrhosis with ascites) was given a weight of 3 and metastatic solid tumor or AIDS received a weight of 6. The specific criteria for Charlson comorbidity score calculation are available from the author.

To create a combined age–comorbidity score, a patient 40 years of age is assumed to have the lowest risk of comorbid death attributable to age and a patient with a Charlson comorbidity index score of 0 also has the lowest risk attributable to comorbid disease. Each decade of age over 40 adds 1 point to risk (e.g. 50–59 years, 1 point; 60–69 years, 2 points; 70–79 years, 3 points) and these points for age are added to the score from the Charlson comorbidity index (e.g., 0, 1, 2, 3, etc.) Thus, a 60-year-old patient with a Charlson comorbidity score of 3 would have a combined age–comorbidity score of 5 and a 50 year old patient with a Charlson comorbidity score of 2 would have an age–comorbidity score of 3.

Long term follow-up

At approximately 3 and 5 years post-operatively, all patients were contacted by a standardized written or telephone interview of the patient. Patients were specifically asked about interval hospitalizations, myocardial infarction, cerebrovascular accident, new onset congestive heart failure or angina pectoris, renal insufficiency and current medications. In several instances, a member of the patient's family was interviewed, when the patient was unavailable. In approximately 20% of cases, patients' physicians were contacted or hospital records reviewed to clarify the patient's status, when necessary and possible.

At the conclusion of follow-up, which began 5 years after the last patient's operation, 11

patients had been completely lost to follow-up. Thus, follow-up was available on 207 of the 218 patients—95% of the patients who survived hospitalization. Only 2 patients had less than 3 year follow-up and 185 patients (89%) had follow-up completed for 5 or more years. The median follow-up was 7.9 years, with a 25th–75th percentile range of 3.9–8.6 years.

For patients who died, the circumstances leading to their death were obtained from telephone interviews with relatives or friends, hospital charts, or their physicians (51 patients) and this information was used to classify the cause of death. For those patients who could not be contacted or located, the National Death Index was employed to ascertain whether they had died. For those patients who had died, death certificates were obtained from the states in which they died. In 25 patients (11%), data was available only from the patient's death certificates and there were no data regarding the patient's history over the 5 year interval after surgery. Therefore the cause of death was ascertainable from the patient's history in 67% of instances.

Data analysis

Kaplan–Meier plots were developed using PROC LIFETEST in SAS [6]. The relationship of age and comorbidity as well as of the combined age–comorbidity score to survival in months was assessed using proportional hazards analysis which was conducted using PROC PHREG in SAS [7]. Age was coded by decade. Age (by decade) and comorbidity were covariates modelled in the analysis. Interaction between age and comorbidity was not a focus of the investigation. The proportional hazards assumption was tested by coding age into decades and also using the Charlson comorbidity scores as blocks. The log–log survival was then plotted versus the median covariate value for each block (e.g. decade of age and comorbidity score) and each resultant plot was combined into one plot. If the proportional hazard assumption is met, such plots are very nearly parallel or at least do not cross, which was the case for the present data set. Thus, the proportional hazards assumption appeared to be justified. The regression coefficients for age and comorbidity were exponentiated from the proportional hazards model providing an assessment of the adjusted relative risk of death as a function of the change in the dependent variable considering the contribution of other covariates. A proportional hazards analysis was subsequently performed for the new combined age–comorbidity score. Confidence intervals were developed by using the standard error of the regression coefficient. The p values were calculated from a multivariate proportional hazards analysis. When age was modelled in yearly increments, the basic results did not change.

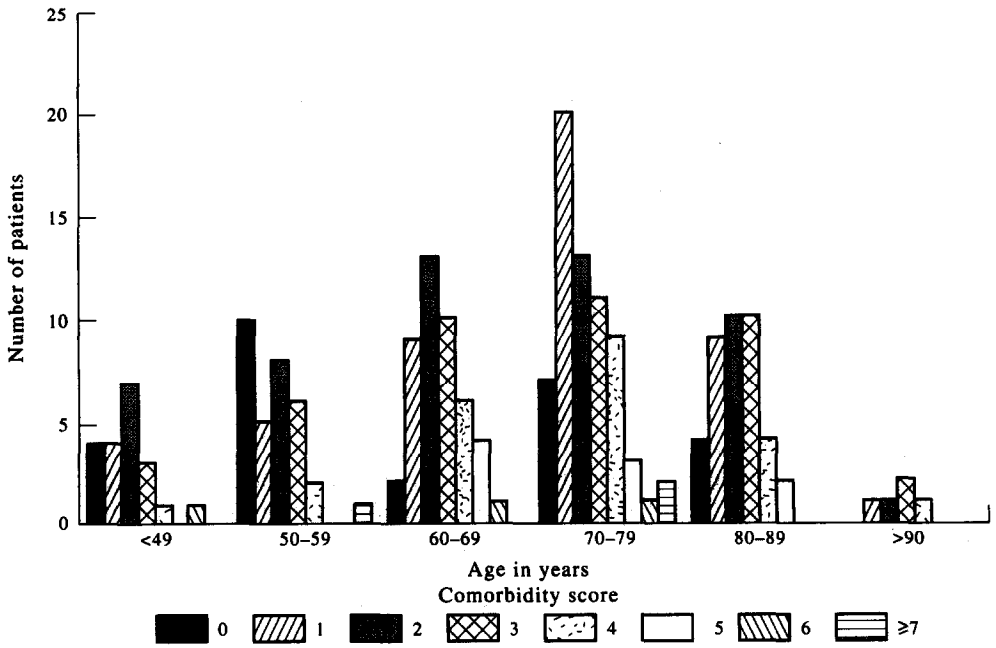

Fig. 1. Distribution of patients according to age and comorbidity.

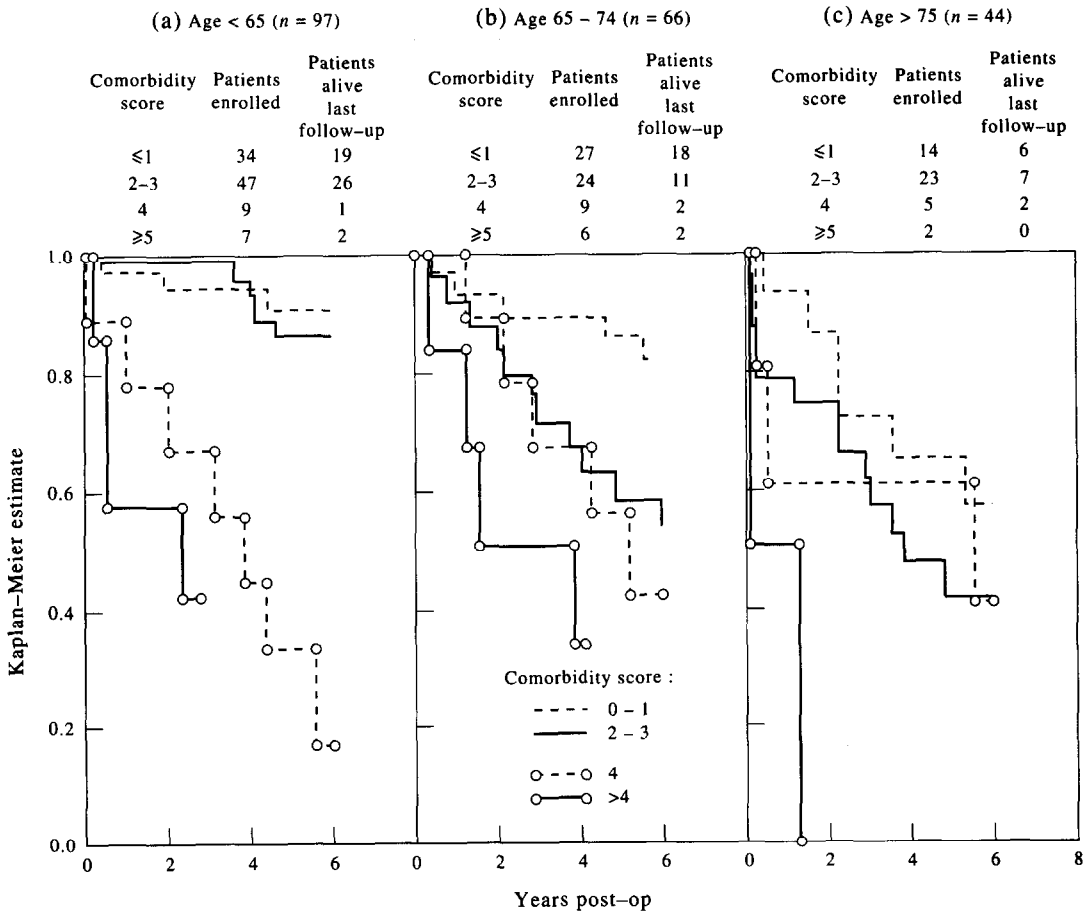

Fig. 2. Survival of patients according to age group and comorbidity scores.

RESULTS

The mean age of the population was 62.9 ± 13.6 years, while the median was 65 years (25th–75th percentile range: 54–73 years). Sixty-three percent of the population were women. The median Charlson comorbidity score was 2 (25th–75th percentile range: 1–3) (Fig. 1). In total, there were 42 cardiovascular deaths including deaths attributable to cardiac causes (30), renal causes (4) and cerebrovascular causes (8). There were also 34 deaths from other non-cardiovascular causes including 19 from metastatic disease, 4 from pneumonia, 2 from chronic pulmonary disease, 4 from sepsis, 4 in the setting of other acute medical or surgical problems and 1 from unknown cause.

Figure 1 shows the distribution of patients according to age and Charlson comorbidity score. The figure shows that each of the age groups contained patients with a range of comorbidity scores.

Validation of the model

Figure 2 shows the Kaplan–Meier estimates of survival functions according to comorbidity score for patients less than 65 years of age [Fig. 2(a)], for those between 65 and 74 years of age [Fig. 2(b)] and for those over 75 years of age [Fig. 2(c)]. The breakdown into these age categories is arbitrary but designed to demonstrate how comorbidity and age can be readily combined. Displaying the data by decades would have produced groups that were too small to analyze statistically. Gender was not included because it was not a significant predictor of mortality.

Figure 3 shows the Kaplan–Meier estimates of survival functions according to combined age–comorbidity score.

Estimation of the proportional hazards regression coefficients

A proportional hazards model was fit to

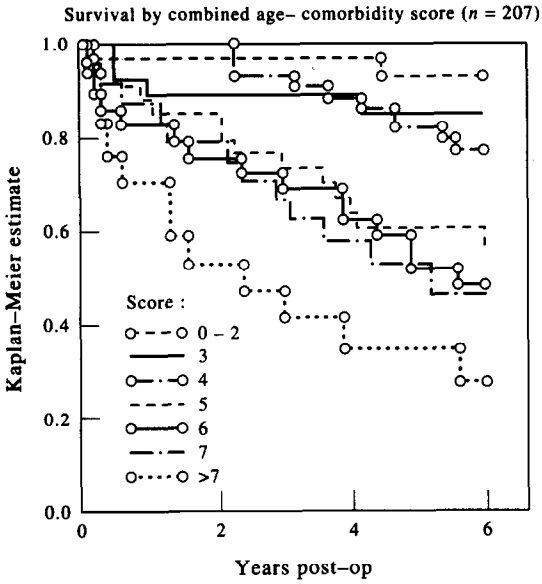

Fig. 3. Survival of patients according to combined age–comorbidity score.

estimate the overall relative risk of death by age and Charlson comorbidity and then for the combined age–comorbidity score. The estimated regression coefficients are shown in Table 1. Table 1(A) shows the estimated relative risk of death by using the regression coefficients obtained simultaneously for age and comorbidity. The relative risk of death for each decade of age was 1.42 (99% confidence interval: 1.08–1.88, $p < 0.001$) and for each increasing comorbidity rank was 1.46 (99% confidence interval: 1.22–1.74, $p < 0.0001$).

The combined age–comorbidity score was a highly significant predictor of prognosis ($p < 0.0001$) when modelled as a single covariate in the proportional hazards model [Table 1(B)]. The 4 patients with a combined age–comorbidity score of 9, the patient with a combined score of 10 and the patient with a combined score of 11 have all been included in the group of patients with a combined age–comorbidity score of $\geqslant 8$. The resulting estimated relative risk for each combined age–comorbidity unit was 1.45 (99% confidence interval: 1.25–1.68).

DISCUSSION

In the original study of comorbidity [1], the Charlson comorbidity index was developed from 1 year follow-up data on an inception cohort of 604 patients admitted to the medical service at New York Hospital during a 1 month period. The index was then tested for its ability to predict risk of death from comorbid disease in a cohort of 685 patients treated for primary breast cancer at Yale New Haven Hospital. In the validation or 'testing' cohort, but not in the developmental or 'training' cohort, age was an important predictor of risk of death. Undoubtedly, in the original study, the longer follow-up of the validation cohort (10 years) versus that of the 'training cohort' (1 year) accounted for greater prognostic importance of age in the validation cohort. In this same study, we had also compared the Charlson comorbidity index to the Kaplan and Feinstein method [8]. Both the Charlson comorbidity index and the Kaplan–Feinstein method were significant predictors of death from comorbid disease and in this original study, yielded similar survival curves.

In the original study, it was proposed that in longitudinal studies with follow-up periods of 5

Table 1(A). Proportional hazards model incorporating decade of age and comorbidity score as two covariates. Estimated relative risk of death and 99% confidence interval

Parameter estimates

	Regression coefficient	Standard error	Chi-Square	*P* Value
Decade of age	0.35	0.11	10.80	<0.001
Comorbidity	0.38	0.07	30.14	<0.0001

Estimated relative risk of death (99% confidence interval)

Comorbidity score	Decade of age				
	40–49	50–59	60–69	70–79	80–89
0	1.00	1.42 (1.08, 1.88)	2.03 (1.25, 6.61)	2.88 (1.25, 6.61)	4.10 (1.36, 12.42)
1	1.46 (1.22, 1.74)	2.08 (1.50, 2.86)	2.96 (1.67, 5.24)	4.21 (1.82, 9.74)	5.99 (1.97, 18.20)
2	2.13 (1.50, 3.04)	3.03 (1.96, 4.70)	4.31 (2.27, 8.19)	6.14 (2.54, 14.88)	8.74 (2.79, 27.43)
3	3.11 (1.83, 5.29)	4.42 (2.46, 7.95)	6.30 (2.99, 13.28)	8.96 (3.43, 23.43)	12.76 (3.84, 42.42)
4	4.54 (2.23, 9.22)	6.46 (3.06, 13.63)	9.19 (3.83, 22.05)	13.08 (4.52, 37.82)	18.65 (5.17, 67.05)

Table 1(B). Proportional hazards model incorporating the combined age–comorbidity score as a single covariate. Estimated relative risk of death and 99% confidence interval

Parameter estimates

	Regression coefficient	Standard error	Chi-Square	*P* Value
Age–comorbidity score	0.37	0.06	42.60	<0.0001

Estimated Relative risk of death (99% confidence interval)

Age–comorbidity score	Estimated relative risk
0	1.00
1	1.45 (1.25, 1.68)
2	2.10 (1.57, 2.81)
3	3.04 (1.96, 4.71)
4	4.40 (2.45, 7.90)
5	6.38 (3.07, 13.24)
6	9.23 (3.84, 22.20)
7	13.37 (4.81, 37.22)
8	19.37 (6.01, 62.40)

years or more, both age and comorbidity should be taken into account as predictors of death from comorbid disease. A method of combining age and comorbidity into a single 'index' was proposed as potentially useful in stratifying results for certain, primarily smaller, studies. For the purposes of univariate, bivariate or multivariate analysis, the effect of age and the effect of comorbidity should be examined separately. For example, in a multivariate analysis designed to assess whether other covariates of clinical interest that may influence outcome, age and comorbidity should be entered as separate variables. However, it is often useful to present longitudinal results stratified according to a single index of risk or risk group. In most such evaluations, both age and comorbidity may have a substantial impact on long term survival. If the study is large, both can be examined separately. If the study is relatively small, it would be helpful to have a method of combining them into a single variable. For example, consider studies reporting on the survival after coronary artery bypass grafting according to the pre-operative ejection fraction. It may be useful to have a way to predict the survival experience of patients by risk due to age and comorbidity. The age–comorbidity index proposed here represents one such alternative.

An important advantage of the combined variable is that one less independent variable is included in the analysis. This is desirable when the number of outcome events is small. It should be noted, however, that smaller studies may also warrant separate analysis of age and comorbidity. The index is intended to be a simple, "crude" combined risk assessment for easy use by the clinician.

This paper serves to confirm the validity of the originally proposed age–comorbidity index. Among subjects in this study, the risk of death from an increase of one in the comorbidity score is of the same order of magnitude as the risk of death from an additional decade of age.

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