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A NEW METHOD OF CLASSIFYING PROGNOSTIC COMORBIDITY IN LONGITUDINAL STUDIES: DEVELOPMENT AND VALIDATION

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Abstract—The objective of this study was to develop a prospectively applicable method for classifying comorbid conditions which might alter the risk of mortality for use in longitudinal studies. A weighted index that takes into account the number and the seriousness of comorbid disease was developed in a cohort of 559 medical patients. The 1-yr mortality rates for the different scores were: "0", 12% (181); "1–2", 26% (225); "3–4", 52% (71); and "≥ 5", 85% (82). The index was tested for its ability to predict risk of death from comorbid disease in the second cohort of 685 patients during a 10-yr follow-up. The percent of patients who died of comorbid disease for the different scores were: "0", 8% (588); "1", 25% (54); "2", 48% (25); "≥ 3", 59% (18). With each increased level of the comorbidity index, there were stepwise increases in the cumulative mortality attributable to comorbid disease (log rank $\chi^2 = 165$; $p < 0.0001$). In this longer follow-up, age was also a predictor of mortality ($p < 0.001$). The new index performed similarly to a previous system devised by Kaplan and Feinstein. The method of classifying comorbidity provides a simple, readily applicable and valid method of estimating risk of death from comorbid disease for use in longitudinal studies. Further work in larger populations is still required to refine the approach because the number of patients with any given condition in this study was relatively small.

I. INTRODUCTION

IN MANY short term studies of therapeutic efficacy, investigators have employed restrictive eligibility criteria to eliminate patients who have comorbid diseases [1]. Restrictive criteria increase the certainty that any observed differences are attributable to the index disease or to the treatment, not to the confounding influence of comorbid disease [1, 2]. However, trials that address whether treatments are efficacious among patients without comorbid conditions have limited generalizability [1, 2].

An alternative approach would be to develop a method of prospectively evaluating the impact of prognostically cogent comorbid conditions at the time of enrollment into the trial. If ailments that posed a significant independent threat to survival were identified, patients with a higher risk of death from comorbid disease might be randomized separately than patients with a lower risk [3]. The only available method for classifying comorbidity was developed by consensual criteria and has not been validated in another population [4].

The objective of this study was to develop a prognostic taxonomy for comorbid conditions which singly or in combination might alter the risk of short term mortality for patients enrolled in longitudinal studies. The comorbidity index was developed empirically, based on the 1-yr mortality from an inception cohort study of 604 patients admitted to the medical service at New York Hospital during 1 month in 1984. The comorbidity index was then tested for its ability to predict risk of death from comorbid disease

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in a cohort of 685 patients who were treated for primary breast cancer at Yale New Haven Hospital between 1962 and 1969. Its performance was compared to the method of classifying comorbid disease developed by Kaplan and Feinstein [4].

II. METHODS

A. "Training" Population

1. Assembly of population

The intended population consisted of all patients admitted to the medical service at New York Hospital–Cornell Medical Center during a 1-month period in 1984. During this period, 607 patients were admitted to the medical service. All 607 patients were evaluated on admission; however, the charts of 3 patients could not be located. Therefore , the initial cohort consisted of 99.3% of those eligible.

2. Data collection

At the time of admission, the admitting resident rated the patients' severity of illness as not ill, mildly ill, moderately ill, severely ill or moribund. As previously described [5], the prospective rating of illness severity was the most significant predictor of in hospital mortality ($p < 0.0001$). The reasons for admission were grouped according to whether the patients had a high or low risk of mortality during hospitalization; the details of the system are published elsewhere [5].

After discharge, the patients' hospital records were reviewed and data were collected about the patients' demographic and clinical characteristics and the subsequent course of the patient, including complications, arrests, deaths, and status at discharge. The number and severity of comorbid diseases at the time of admission were recorded.

3. Follow-up

Complete 1-yr follow-up information was obtained for 93% (559/604) of the patients studied. The principal source of follow-up information was the attending physician who admitted the patient or who referred the patient for admission. If the patients had not been seen in follow-up, they were contacted directly by telephone, if possible, or by letter. Vital statistics' registries were also searched, when feasible. The 45 patients for whom no follow-up information was available tended to be younger, less sick, and to have fewer, less severe comorbid disease. Eight of these patients had initially been admitted for problems related to alcohol or drug abuse. Fifteen of the patients had no telephone and mail was returned address unknown. Vital statistics bureaus were contacted when letters were not returned and 3 deaths were confirmed.

Survival was measured in months from the date of admission to the hospital (zero time) to the date of death or to 1 yr after admission; therefore, except as noted in the results, deaths that occurred in-hospital were counted as part of the 1-mortality rates. As is customary, the patients who were lost to follow-up prior to 1 yr were considered as withdrawn alive as of the last date of follow-up for life table analysis.

B. "Testing" Population

1. Assembly of population

The cohort consisted of all 685 women with histologically proven primary carcinoma of the breast, who received their first treatment at Yale New Haven Hospital between 1 January 1962 and 31 December 1969.

2. Data collection

From medical records and other sources of data, a chronology of each patient's illness was compiled. It included the anatomic stage, the nodal status and histologic type, menstrual status, symptomatic status, and the clinical rate of disease progression [6]. The number and severity of comorbid diseases were also noted.

3. Follow-up

Complete follow-up information was obtained for all but one of the patients at 5 yr, and for all but four of those eligible for 10-yr follow up at the closing date of the study. The mode of death was determined from clinical information leading to the patient's death. Deaths were then attributed as due either to breast cancer or to comorbid disease. In the analysis presented, the 20 patients who had visceral metastases at death, but whose death was caused by a comorbid condition (e.g. myocardial infarction) were categorized as cancer deaths. Thus, to be cited as a comorbid death, the patient must have been free from metastatic disease at the last examination performed before the time of death. Survival in months was calculated from the start of anti-neoplastic therapy to the primary site or if no such treatment was given, from the date of the first therapy to a metastatic site.

C. Classification of Cormorbidity

All comorbid diseases were recorded. Conditions that had completely resolved (i.e. history of pneumonia) or a history of operation for currently inactive conditions (i.e. history of cholecystectomy) were not counted as comorbid diseases. In this analysis, a patient was classified according to each comorbid disease that they had, so that a patient with chronic liver disease and angina would be classified in both categories. For the more common conditions, such as ischemic heart disease, diabetes, hypertension, data were collected characterizing the disease seriousness. For rare conditions, such as multiple sclerosis, no such date on the seriousness of the disease was collected. The conditions that were considered prognostically cogent are defined in the Appendix.

D. Statistical Analysis

In cancer studies, deaths attributable to comorbid disease are handled as if the patient was withdrawn alive at the time of death [7]. In this study, however, deaths attributable to comorbid conditions were the outcome of interest. Therefore, in the testing population, survival rates were calculated by the life table method, with cancer deaths handled by regarding the patient as withdrawn alive at the time of death. The statistical difference between mortality rates was examined by the chi-square test, calculated by the log rank method [8].

The relationship of potential prognostically important variables to survival (in months) in both the training and testing population was assessed using Cox's regression method for life-table data [9]; this proportional hazards analysis was performed using the PHGLM procedure available in SAS [10]. The R statistic is similar to the multiple correlation coefficient and R^2 is approximately equal to the explained variance. Partial Rs are also calculated for each variable in the model. The stepwise procedure was used and dummy variables were set up for nominal data. Comorbid diseases were coded as 0 = absent; 1 = present, as were other nominal covariates. Severity was coded as 1 = not ill, 2 = mildly ill, 3 = moderately ill, 4 = severely ill, and 5 = moribund. Age was coded in decades.

Unadjusted relative risks (which assess the risk of mortality for patients with a given comorbid condition, regardless of the presence of other comorbid diseases, the severity of illness or the reason for admission) are calculated as the proportion of patients with the condition who died divided by the proportion of patients without the disease who died. In contrast, the adjusted relative risks estimate the risk of death with a given comorbid condition controlling for the contribution of all coexistent comorbid diseases as well as illness severity and reason for admission. These adjusted relative risks were calculated from the beta coefficients generated by the stepwise backward proportional hazards model, as the ratio of those with the disease to those without [11].

To facilitate the use of the comorbidity index in prospective studies, the method of Hutchinson and Thomas was used to create a scoring system that combined both age and comorbidity [12]. The relative risks for each calculated from the proportional hazards model were used to create a single prognostic variable combining age and comorbidity that is indicative of subsequent risk. Thus, a composite comorbidity-age score was calculated for each patient and the actual 10-yr survival was evaluated. The predicted survival was calculated using a theoretical low risk population, whose 10-yr survival was 98.3%. If the combined score was 3, the calculation was

$$e^{0.9\ (\text{comorbidity} - \text{age score} = 3)} = e^{2.7} = 14.8,$$

and the predicted survival was $0.983^{14.8} = 0.776$.

III. RESULTS

A. Development of Comorbidity Index

1. Prognostic impact of individual comorbid diseases at 1 yr

Table 1 shows the in-hospital and 1-yr mortality rates for patients with different comorbid diseases. The in-hospital mortality rates for patients are shown in the first column. The second column shows the 1-yr mortality rates for patients with different comorbid diseases as well as the number of patients with each condition for whom 1-yr follow-up data was available. The proportion of patients who were lost to follow-up was similar (7%) for most comorbid conditions.

One-year mortality rates were significantly higher for patients with any oncologic condition and for acquired immune deficiency syndrome; the p values calculated from the proportional hazards model are shown in Table 1. Additionally, patients with moderate to severe liver disease and those who were hemiplegic or paraplegic regardless of cause also had significantly increased mortality at 1-yr. Patients with

Table 1. Individual comorbid diseases: mortality during hospitalization and at 1 yr

	Percent in-hospital mortality	Percent 1-yr mortality		1-yr unadjusted relative risk	1-yr adjusted relative risk†
Myocardial					
Angina	5 (100)	14 (93)		0.4	0.6
Arrhythmia	11 (56)	31 (52)		0.9	1.2
Valvular	6 (31)	32 (28)		0.9	1.1
Myocardia infarction	10 (72)	34 (71)		1.0	1.4
Congestive heart failure	13 (80)	32 (77)		1.0	1.3
Vascular					
Hypertension	11 (161)	28 (151)		0.8	1.0
Peripheral vascular	13 (31)	30 (30)		0.9	1.3
Cerebrovascular	6 (35)	31 (29)		0.9	1.4
Pulmonary					
Mild	10 (63)	46 (61)		1.4	1.3
Severe–moderate	16 (25)	52 (25)	$p = 0.1$	1.6	1.4
Neurologic					
Other neurologic	11 (27)	36 (25)		1.1	1.2
Dementia	10 (20)	47 (19)		1.4	1.4
Hemiplegia (paraplegia)	20 (15)	60 (15)	$p = 0.05$	1.8	1.9
Endocrine					
Other endocrine	0 (11)	36 (11)		1.0	1.2
Diabetes	16 (37)	29 (35)		1.1	1.4
Diabetes with end organ	0 (13)	54 (13)	$p = 0.06$	1.6	1.9
Renal					
Mild insufficiency	8 (12)	25 (12)		0.7	0.5
Moderate to severe	8 (26)	58 (26)	$p = 0.09$	1.8	1.5
Liver					
Mild	22 (9)	55 (9)		1.7	1.4
Moderate to severe	23 (13)	64 (11)	$p < 0.01$	1.9	2.9
Gastrointestinal					
GI bleeding	9 (22)	32 (19)		0.9	0.7
Inflammatory bowel	5 (12)	30 (10)		0.9	1.1
Peptic ulcer	19 (32)	48 (31)		1.5	1.4
Cancer/immune					
Tumor	13 (39)	50 (36)	$p < 0.01$	1.5	2.1
Lymphoma	10 (31)	57 (30)	$p < 0.001$	1.7	2.4
Leukemia	5 (19)	55 (18)	$p < 0.01$	1.7	2.2
AIDS	33 (18)*	82 (17)	$p < 0.0001$	2.6	6.3
Metastatic cancer	31 (54)**	87 (52)	$p < 0.0001$	3.0	7.4
Miscellaneous					
Rheumatologic	14 (22)	29 (21)		0.8	1.4
Coagulopathy	29 (7)	73 (7)		2.1	1.1

Once illness severity and the reason for admission were taken into account, only two conditions—AIDS and metastatic solid tumor—were significant predictors of in-hospital mortality [5].
†Calculated from the proportional hazards model. Number of patients in parentheses. *$p < 0.01$; **$p < 0.001$.

diabetes with end-organ damage, those with moderate to severe renal disease, and those with moderate to severe pulmonary disease also had increased mortality rates; however, the p values for each were >0.05 but >0.1.

2. The overall burden of comorbid disease

(*a*) *The number of comorbid diseases.* The next objective was to assess the impact of combinations of comorbid diseases on one year mortality. The simplest and most obvious tactic for estimating the overall burden of comorbid disease would be to find the total number of individual comorbid diseases for each patient. When each distinct condition listed in Table 1 was counted, the mean number of comorbid diseases per patient was 1.68 ($\pm$ 1.94 SD), with a range of 0–13. Table 2 shows the 1-yr mortality rates according to the number of comorbid diseases, illness severity and reason for admission (low risk vs high risk). In fact, the total number of comorbid diseases did predict 1-yr mortality ($p < 0.05$), as did illness severity-reason groups, the major differences were between those patients without comorbid conditions and those with one or more.

This approach to measuring the burden of comorbid disease assumes that a patient with leukemia has the same burden of comorbid disease as a patient with renal disease.

Table 2. One year mortality rates according to number of comorbid conditions, illness severity and reason for admission

Severity and reason for admission	Number of comorbid diseases, in percent			
	"0"	"1–2"	"3–4"	"> 5"
Not to mildly ill				
Low risk	10 (52)	21 (109)	21 (14)	13 (8)
High risk	7 (15)	37 (22)	50 (6)	100 (2)
Moderately ill				
Low risk	6 (18)	27 (62)	38 (16)	100 (2)
High risk	19 (16)	39 (31)	62 (13)	33 (6)
Severely ill				
Low risk	30 (10)	42 (52)	38 (13)	67 (6)
High risk	50 (10)	71 (49)	73 (15)	89 (9)
Total	15 (121)	38 (326)	45 (77)	74 (33)

Model $\chi^2 = 95.92$; $df = 3$, $R = 0.195$; $\log (h_i/h_o) = 0.52$ (± 0.08) severity + 0.53 (± 0.15) reason + 0.06 (± 0.03) number of comorbid diseases, where h_i/h_o is the hazard with the characteristic divided by the hazard without. The standard error of the beta coefficient is listed as ($\pm$).

Intuitively, this is problematic. In fact, among the 208 patients with one comorbid disease, 70 had an oncologic problem. These patients had a 1-yr mortality of 66%, significantly higher than the 19% among patients without such conditions ($\chi^2 = 47$; $p < 0.001$). Therefore, it is obvious that a system that weights each disease identically fails to capture important prognostic differences. In effect, this approach does not take into account the seriousness of a comorbid disease. Therefore an alternate method was explored.

(*b*) *The number and seriousness of comorbid diseases: a weighted index.* A weighted index was developed that takes into account both the number and the seriousness of comorbid diseases. The adjusted relative risks (shown in Table 1) were employed as weights for the different comorbid diseases. Conditions with relative risks of 1.2 or less were dropped from consideration. The exact relative risks were used in the first analysis, but the results did not differ importantly if the weights were rounded to the nearest digit. To simplify the system, conditions with a relative risk $\geqslant 1.2 < 1.5$ were assigned a weight of 1; conditions with a risk $\geqslant 1.5 < 2.5$ a weight of 2; conditions with a weight of $\geqslant 2.5 < 3.5$ a weight of 3; and those two conditions with weights of 6 or more were assigned a weight of 6. The components of the weighted index is shown in Table 3. The analysis was performed in two ways; first, with the total index (i.e.) all conditions with a relative risk of 1.3 or more and secondly with only those conditions which had a significant or near significant (i.e. $p < 0.1$) independent impact on mortality. The results were quite similar and only the results of the first analysis are reported.

Table 4 shows the 1-yr mortality rates according to the weighted index of comorbid disease, illness severity and reason for admission. The weighted index of comorbidity was a significant predictor ($p < 0.0001$) of 1-yr survival; as were illness severity and reason for admission. This model explained a higher proportion of the variance than the model based on the number of comorbid diseases. The stepwise increase in mortality within severity and reason groups with a higher comorbidity index was also more impressive. The mortality rates among patients with an index 5 or more were especially high.

A further tactic involved restricting the analysis only to those patients who survived hospitalization (i.e. the 66 patients who died

Table 3. Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).

Table 4. Percentage 1-yr mortality according to severity, reason and the scores from the weighted index of comorbidity

Severity and reason for admission	Weighted index of comorbidity			
	"0"	"1–2"	"3–4"	"> 5"
Not to mildly ill				
Low risk	7 (82)	14 (68)	29 (14)	60 (20)
High risk	5 (18)	21 (19)	100 (3)	100 (5)
Moderately ill				
Low risk	7 (30)	19 (44)	38 (13)	91 (11)
High risk	16 (19)	28 (22)	50 (14)	73 (11)
Severely ill				
Low risk	26 (19)	33 (39)	36 (11)	100 (14)
High risk	38 (13)	58 (33)	94 (16)	100 (21)
Total	12 (181)	26 (125)	52 (71)	85 (82)

$\chi^2 = 207.8$; $df = 3$; $R = 0.295$; log $(h_i/h_o) = 0.50$ (± 0.08) severity + 0.45 (± 0.15) reason + 0.329 (± 0.03) weighted comorbidity score.

in-hospital were eliminated). Among such patients, the weighted index of comorbidity ($p < 0.0001$) and illness severity ($p < 0.001$) were both significant predictors of mortality at 1 yr after admission, although reason for admission was not. The 1-yr mortality rates are shown in Table 5. There is a stepwise increase in the observed mortality with a higher comorbidity index, within each of the severity groups.

B. Validation of the Comorbidity Index

In this cohort of breast cancer patients, the prevalence of comorbid disease was significantly lower than in the cohort of medical patients. For example, 86% of the 588 breast cancer patients had comorbidity index scores of zero; in contrast, only 29% of medical patients had an index of "0" ($p < 0.001$). Eight percent of the breast cancer patients had an index of 1; 4% of 2; and 3%, of 3 or more. The 1-yr survivals were greater in this population (i.e. 99, 94, 84 and 69%) than in the "training" population. By 10 yr, 83 of the 685 patients in the second population died of comorbid disease: 12 by the end of the 1st year, an additional 27 by the end of the 5th year; and an additional 44 by 10 yr.

None of the variables that predicted survival in the cohort as a whole—TNM stage, nodal status, clinical rate of growth or menstrual status—was a significant predictor of death from comorbid disease, except age. Therefore among all of the clinical and demographic variables, only two were significant predictors of risk of comorbid death—age and comorbidity ($p < 0.0001$ for both). The adjusted relative risks were calculated from the beta coefficients. The relative risk for each increasing level of the comorbidity index was 2.3 (95% confidence limits: 1.9–2.8) and for each decade of age was 2.4 (95% confidence limits: 2.0–2.9). In essence, each decade of age and each rank of comorbidity added a similar risk; specifically, the risk of dying from comorbid disease posed by an additional decade of age was equivalent to an increase of 1 in the comorbidity index.

In the training study, age had not been a predictor of death from comorbid disease; this was not surprising because the follow-up period was only 1 yr. As shown in the testing population, age became an important predictor of the

Table 5. Percentage 1-yr mortality among patients who survived hospitalization according to illness severity and weighted index of comorbidity*

Severity	Weighted index of comorbidity			
	"0"	"1–2"	"3–4"	"> 5"
Not to mildly ill	7 (97)	16 (87)	41 (17)	64 (22)
Moderately ill	6 (47)	17 (63)	39 (25)	76 (17)
Severely ill	12 (25)	30 (57)	50 (18)	100 (15)
Total	7 (169)	21 (207)	43 (60)	78 (54)

*Reason for admission was not a significant predictor of mortality in this group of patients.

$\chi^2 = 139$; $df = 2$; $R = 0.301$; log $(h_i/h_o) = 0.36$ (± 0.09) severity + 0.42 (± 0.03) weighted comorbidity score.

Table 6. Ten-year actual and predicted survival according to age-comorbidity in the testing population

Comorbidity–age combined risk score*	Number of patients	Actual 10-yr survival (%)	Predicted 10-yr survival† (%)
0	213	99	99
1	156	97	96
2	136	87	90
3	109	79	77
4	42	47	53
5	29	34	21

*Each comorbidity rank was equivalent to one decade of age, with 40 yr taken as the zero rank for age (e.g. a patient who was 50 who had a comorbidity index of 2 would have a score of 3). The beta coefficient for the age–comorbidity combined score was 0.9 (e.g. <40 coded as 0, 50 as 1, 60 as 2, 70 as 3, etc.).

†The predicted survival was calculated from the 10-yr survival of a theoretical low risk population (0.983). Thus for a score of 70 the calculation was $0.983^{14.8}$, where $14.8 = e^{2.7} = e^{0.9(3)}$.

risk of death attributable to comorbid disease, independent of pre-existing comorbid conditions with longer follow-up. Therefore, in longitudinal studies with follow-up periods of 5 yr or more, both age and comorbidity should be taken into account as predictors of death from comorbid disease. One method for practically accomplishing this involves creating a combined age–comorbidity variable [12]. Using this approach, a patient 40 yr of age would be assumed to have no risk of comorbid death attributable to age and a patient with a comorbidity index score of 0 would have no risk attributable to pre-existing comorbid disease. Each decade of age over 40 would add 1 point to risk (i.e. 50 yr, 1; 60 yr, 2; 70 yr 3; etc.) and the "age points" would be added to the score from the comorbidity index (i.e. 0, 1, 2, 3, etc.). Thus, a patient 60 yr (i.e. 2 points) with a comorbidity score of 1 would be rated as 3, or a patient 60 yr of age with a comorbidity score of 3 would be rated as 5. The "risk scores" were calculated for each patient and are shown with the actual 10-yr survival rates in Table 6. The predicted survivals were calculated using a theoretical low risk population [12]. The actual survival and the estimated survivals are quite close except in the worst prognostic strata.

C. Weighted Comorbidity Index vs Kaplan and Feinstein Method

Figure 1 shows the survival curves for the "testing" population stratified according to the weighted index of comorbidity; specifically, "0" denotes patients with an index of zero; "1", of one, etc. With a higher index, there was a

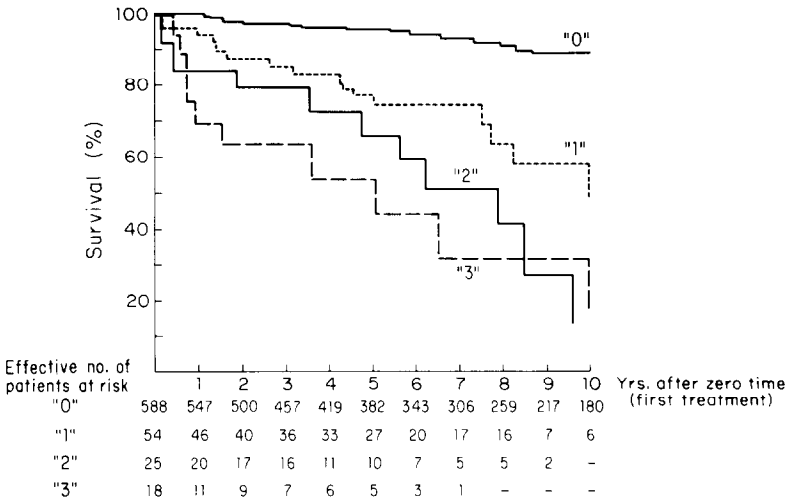
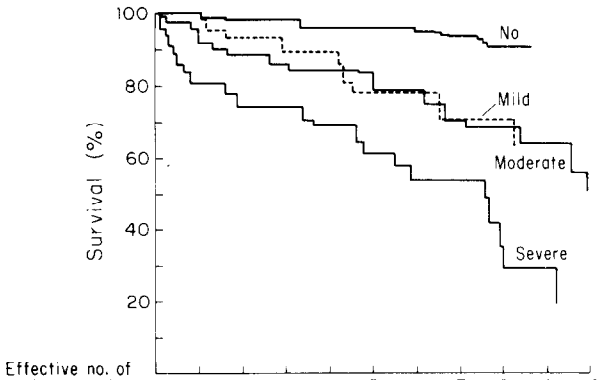


Fig. 1. Cumulative survival according to weighted index of comorbidity for patients in the validation study. Proportional hazards: $\chi^2 = 165.71$; $df = 2$; $p < 0.0001$; $R = 0.406$; $\log (h_i/h_o) = 0.836\ (\pm 0.103)$ comorbidity score $+ 0.862\ (\pm 0.096)$ age in decades.



Effective no. of patients at risk	1	2	3	4	5	6	7	8	9	10	Yrs. after zero time (first treatment)
No	550	512	471	432	393	359	324	289	247	207	175
Mild	36	33	26	24	23	18	13	12	9	6	5
Moderate	56	51	43	39	32	28	25	19	14	12	8
Severe	43	29	26	23	21	17	14	10	4	2	1

Fig. 2. Cumulative survival according to Kaplan and Feinstein method of ranking comorbidity for patients in the validation study. Proportional hazards: $\chi^2 = 164.91$; $df = 2$; $p < 0.0001$; $R = 0.405$; log $(h_i/h_o) = 0.685$ (± 0.093) comorbidity score + 0.839 (± 0.099) age in decades.

significant decrease in survival (log rank $\chi^2 = 163$; $p < 0.0001$). At 10 yr, the survival rates in the four strata were: 93, 73, 52 and 45%.

The data was also analyzed according to the method for staging comorbidity developed by Kaplan and Feinstein [4]. This system ranked 5% of the patients as having mild comorbidity, 8% as moderate, and 6% as severe; 80% of the patients had none. Figure 2 shows the cumulative survival rates for breast cancer patients rated as having no, mild, moderate or severe comorbidity by this alternate method. With increasing ranks, there was an increase in the mortality rates from comorbid disease; the differences between the comorbidity groups were significant by the log rank test ($\chi^2 = 148$; $p < 0.0001$). Proportional hazards analysis revealed that the Kaplan method was a significant predictor of death from comorbid disease, as was age ($p < 0.0001$ for both). The adjusted relative risk for each increased comorbidity rank was 2.0 (95% confidence interval: 1.6–2.4) and for each decade of age was 2.3 (95% confidence interval: 1.8–2.8). At 10 yr, the survival rates in the strata were: 94, 78, 72 and 51%.

Comparing the survival curves from the weighted index and the Kaplan–Feinstein methods, both methods did well in demarcating those patients at a very low risk of comorbid death. The severe strata in the Kaplan–Feinstein method had a survival experience similar to patients in groups 2 and 3 in weighted index. The amount of variance explained was virtually identical with both methods.

IV. DISCUSSION

Investigators embarking on longitudinal studies invariably confront the issue of whether patients with comorbid disease should be included. In many prospective studies, investigators have employed restrictive eligibility criteria in order to limit the potential that deaths attributable to comorbid disease will confound the evaluation of outcomes. Eliminating patients with comorbid conditions from studies may also increase the efficiency of a trial (i.e. the chance of finding a difference between treatments, if one exists). However, such restrictions result in substantial losses of patients prior to randomization and limit the generalizability of the results [1]. Furthermore, overly stringent eligibility criteria may make it difficult to recruit sufficient numbers of patients [1].

An alternate approach would classify patients with comorbid diseases according to their risk of death from those diseases at the time of enrollment into the study. Patients at greater risk could be evaluated or randomized separately. Although the prognostic significance of comorbid conditions has been documented in some diseases [12], there are only two broadly applicable methods for rating comorbid diseases in terms of their likely prognostic impact. One is the method of Kaplan and Feinstein, developed by consensual criteria for use in a longitudinal study of diabetics [4]. The other, developed empirically from 1-yr mortality from an inception cohort of patients admitted to the medical service for a wide variety of problems,

is the method reported here. Both methods were validated in breast cancer patients, a population with a low incidence of comorbid disease. It should be noted that the weighted index was developed using 1-yr survival, and tested for its ability to predict survival over 10 yr. Given this, its performance was surprisingly good. The power of the method may have been underestimated by counting patients with metastatic cancer who died from comorbid diseases as cancer deaths. Both methods worked equally well in identifying patients at an especially low to high risk of a subsequent cormorbid death. It is of note that a method developed by clinical judgment and one by empiric means had such similar performance.

Both methods are easy to use and involve assessing the presence or absence of certain comorbid conditions as well as their severity. While the Kaplan and Feinstein system ranks patients as having grades of 0–3 according to the single worst condition, our weighted index assigns weights of 1, 2, 3 and 6 for each of the existing comorbid diseases to derive a total score. In most clinical studies, it will not be possible to stratify patients into more than two comorbidity groups. However, the comorbidity scores can be used differently depending on the disease under study. For example, if the disease under study has a low mortality, it might be appropriate to randomize patients with scores of 0 to one group and those with scores of 1 or more to another. If the mortality in the disease is high, a cut-off of 2 or 3 might be selected. The actual cut-off selection would depend on the mortality in the index disease and on the projected duration of follow-up. The magnitude of risk for the different comorbidity strata reported here can be used as a guideline for selecting cut-offs.

While this study is the first that tackles the issue of validating a method of measuring the prognostic impact of comorbid disease, it cannot be viewed as the final, definitive study because the number of patients with any given level of seriousness of a comorbid disease is relatively small. Clearly, both methods require further evaluation in much larger populations in order to make any final or definitive statement about their utility; for example, the numbers of patients with some conditions are small and the number of patients with a given level of seriousness of comorbid disease may also be small. For this reason, both the methods have to be viewed as preliminary. Nonetheless, this study presents evidence that the use of either method is better for purposes of prognostic stratification than simply counting the number of comorbid diseases. Further, this study provides a methodologic approach which may prove useful to others tackling this problem.

To facilitate the use of the comorbidity index in prospective studies, we applied the method developed by Hutchinson and Thomas in their study of prognosis in chronic renal failure [12]. In short, the relative risks calculated from the beta coefficients calculated by the proportional hazards model are used to create a single prognostic variable, indicative of subsequent risk, in this instance, combining the risk of age and the risk of comorbid disease in contributing to the risk of dying from comorbid disease. It should be emphasized that this study has validated both the weighted index and the Kaplan and Feinstein method of ranking comorbidity, but the comorbidity–age composite strategy has not been validated. Nonetheless this composite score performed well when observed vs predicted 10-yr survival was compared. Survival was underestimated in the worst prognostic groups. The prognostic impact of age is a function of the total length of the contemplated follow-up. In studies involving less than 5 yr of follow-up, age may not be a significant predictor of mortality. Therefore, in studies with a short length of follow-up, the age equivalence index will probably not be useful. On the other hand, the comorbidity index or the alternate Kaplan and Feinstein method would be valid methods of estimating risk of death from comorbid disease in shorter studies.

Even when patients are randomized within comorbidity strata, patients in low risk groups may die of comorbid disease. Similarly, the use of restrictive eligibility criteria does not eliminate the problem of comorbid deaths. Although both tactics limit the potential that comorbidity will confound the results, the occurrence of a comorbid death still presents an important methodologic problem. Some investigators argue that deaths due to comorbid disease should be attributed to the assigned therapy (intention to treat), while others argue that the patient should be considered as lost to follow-up at the time of death (pragmatic) [6]. Both methods have drawbacks: the first may obscure treatment effects, while the second may reduce the total number of patients and the power of the study. Newer methods of handling competing causes of failure may provide a solution to this

problem [13]. Nonetheless, prospective methods of evaluating risk of death from comorbid disease should remain useful.

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APPENDIX

The one year mortality [%] and the total number of patients with each condition (n) for whom data was available at one year for the "training study" are listed in parentheses. The same definitions were applied to the "testing" study.

Angina includes patients with chronic exertional angina [13% (70)], those who had coronary artery bypass graft [0% (8)], and those initially admitted with unstable angina [16% (18)].

Myocardial infarction includes patients with one or more definite or probable myocardial infarctions; these patients had been hospitalized and had electrocardiographic and/or enzyme changes. Patients with electrocardiographic changes along were not designated as having had an infarction. The mortality rates were: 1 infarct [35% (53)]; 2 infarcts [23% (13)]; 3 or more infarcts [40% (5)].

Congestive heart failure includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical examination) to digitalis, diuretics, or afterload reducing agents. It does not include patients who are on medication but have had no syptomatic response and no evidence of improvement of physical signs [10% (77)].

Arrhythmia includes patients with chronic atrial fibrillation or flutter [36% (33)], sick sinus syndrome [29% (7)], or ventricular arrhythmias requiring chronic treatment [13% (16)].

Valvular disease includes patients with hemodynamically significant aortic stenosis and/or insufficiency [44% (9)], those with significant mitral stenosis and/or insufficiency [13% (8)], and those with prosthetic aortic or mitral valves [43% (7)] and those with symptomatic mitral valve prolapse, asymmetric septal hypertrophy requiring treatment, or tricuspid insufficiency [25% (4)].

Peripheral vascular includes patients with intermittent claudication or those who had a bypass for arterial insufficiency [4% (24)], those with gangrene or acute arterial insufficiency [25% (4)], and those with an untreated thoracic or abdominal aneurysm (6 cm or more) [50% (2)].

Hypertension includes patients with diastolic pressures over 120 mm Hg [33% (6)]; those with diastolic pressures between 100 and 120 [27% (22)]; and those with diastolic pressures between less than 100 as well as controlled hypertensives [28% (123)].

Cerebrovascular disease includes patients with a history of a cerebrovascular accident with minor or no residua and transient ischemic attacks [(31%) (29)].

Paralysis includes patients with the dense hemiplegia or paraplegia, whether it occurred as a result of a cerebrovascular accident or other condition [60% (15)].

Dementia includes patients with chronic cognitive deficit [47% (19)].

Other neurologic conditions includes patients with Parkinson's disease [40% (5)], uncontrolled seizures [36% (11)], or syncope without an identified cause or treatment [33% (9)].

Mild pulmonary disease includes patients who are dyspneic with moderate activity without treatment or those who are dyspneic only with attacks (e.g. asthma) [46% (61)]. Moderate pulmonary disease includes patients who are dyspneic with slight activity, with or without treatment and those who are dyspneic with moderate activity despite treatment [55% (9)]. Severe pulmonary disease includes patients who are dyspneic at rest, despite treatment, those who require constant oxygen, those with CO_2 retention and those with a baseline PO_2 below 50 torr [50% (16)].

Severe diabetes includes patients with retinopathy, neuropathy, or nephropathy [54% (13)]. Moderate diabetes includes patients who had previous hospitalizations for ketoacidosis, hyperosmolar coma, or control and those with juvenile onset or brittle diabetics [13% (8)]. Mild diabetes includes all other diabetes treated with insulin or oral hypoglycemics, but not diet alone [33% (27)].

Other endocrine includes patients with hypopituitarism [0% (1)], adrenal insufficiency [33% (9)], and recurrent acidosis [100% (1)].

Severe renal disease includes patients on dialysis, those who had a transplant, and those with uremia [50% (5)]. Moderate renal insufficiency includes patients with serum creatinines of >3 mg% [62% (21)]. Mild renal includes those with serum creatinines of 2–3 mg% [25% (12)].

Severe liver disease consists of patients with cirrhosis, portal hypertension and a history of variceal bleeding [50% (6)]. Moderate liver disease consists of cirrhosis with portal hypertension, but without bleeding [80% (5)], and mild liver disease consists of cirrhosis without portal hypertension or chronic hepatitis [55% (9)].

Inflammatory bowel disease includes patients with ulcerative colitis or regional enteritis [30% (10)].

Peptic ulcer disease includes patients who have required treatment for ulcer disease, including those who have bled from ulcers [48% (31)].

Gastrointestinal bleeding includes those who have had

bleeding requiring transfusions from causes other than ulcer disease [32% (19)].

Acquired immune deficiency syndrome includes patients with define or probable AIDS, i.e. AIDS related complex [82% (17)].

Lymphoma includes patients with Hodgkins [50% (2)], lymphosarcoma [75% (4)], Waldenstrom's macroglobulinemia [0% (2)], myeloma [67% (3)], and other lymphomas [58% (19)].

Leukemia includes patients with acute [80% (5)] and chronic [40% (5)] myelogenous leukemia, acute [100% (1)] and chronic [50% (6)] lymphocytic leukemia, and polycythemia vera [0% (1)].

Metastatic cancer includes patients with metastatic solid tumors, including breast [83% (12)], lung [90% (10)], colon [100% (5)] and other tumors [85% (25)].

Tumor consists of patients with solid tumors without documented metastases, but initially treated in the last five years, including breast [75% (4)], colon [53% (7)], lung [67% (3)], and a variety of other tumors [41% (22)].

Rheumatologic disease includes patients with systemic lupus erythematous [0% (2)], polymyositis [0% (2)], mixed connective tissue disease [1000% (1)], polymyalgia rheumatica [0% (1)], and moderate to severe rheumatoid arthritis [42% (12)].

Coagulopathy includes patients with a circulating anticoagulant [67% (3)], or other coagulopathy [75% (4)].