

IMPACT OF COMORBIDITY ON LUNG CANCER SURVIVAL

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Lung cancer is associated with smoking and age, both of which are associated with comorbidity. We evaluated the impact of comorbidity on lung cancer survival. Data on 56 comorbidities were abstracted from the records of a cohort of 1,155 patients. Survival effects were evaluated with Cox regression (outcome crude death). The adjusted R^2 statistic was used to compare the survival variation explained by predictive variables. No comorbidity was observed in 11.7% of patients, while 54.3% had 3 or more (mean 2.97) comorbidities. In multivariate analysis, 19 comorbidities were associated with survival: HIV/AIDS, tuberculosis, previous metastatic cancer, thyroid/glandular diseases, electrolyte imbalance, anemia, other blood diseases, dementia, neurologic disease, congestive heart failure, COPD, asthma, pulmonary fibrosis, liver disease, gastrointestinal bleeding, renal disease, connective tissue disease, osteoporosis and peripheral vascular disease. Only the latter was protective. Some of the hazards of comorbidities were explained by more directly acting comorbidities and/or receipt of treatment. Stage explained 25.4% of the survival variation. In addition to stage, the 19 comorbidities explained 6.1%, treatments 9.2%, age 3.7% and histology 1.3%. Thirteen uncommon comorbidities (prevalence <6%) affected 21.2% of patients and explained 3.5% of the survival variation. Comorbidity count and the Charlson index were significant predictors but explained only 2.5% and 2.0% of the survival variation, respectively. Comorbidity has a major impact on survival in early- and late-stage disease, and even infrequent deleterious comorbidities are important collectively. Comorbidity count and the Charlson index failed to capture much information. Clinical practice and trials need to consider the effect of comorbidity in lung cancer patients.

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Key words: lung cancer; comorbidity; treatment; survival; prognosis

Lung cancer is the leading cause of cancer death in men and women in the United States; in the year 2001, there were an estimated 169,500 new cases and 157,400 deaths due to lung cancer.¹ Approximately 8% of men and 6% of women in the United States develop lung cancer,² and approximately 90% of lung cancers have been attributed to cigarette smoking.^{2,3} The prognosis for lung cancer patients is poor, with crude 5-year survival proportions being approximately 13–15%; survival has improved little over the last 25 years.^{2,4}

Comorbidity is the occurrence of concomitant disease in addition to an index disease of interest or the simultaneous occurrence of multiple diseases in an individual. Lung cancer is associated with age and smoking, and both age^{5,6} and smoking^{7,8} are strongly associated with comorbidity. Thus, it is expected that comorbidity has an important impact in lung cancer patients, yet to date comorbidity has not been well studied in this population. In studies of breast, endometrial, prostate, colorectal and head-and-neck cancer patients, comorbidity has had a negative impact on several health outcomes, including treatment aggressiveness and response as well as survival.^{9–19} The common perception that most lung cancers are rapidly progressive and, as a consequence, almost all lung cancer patients die from their disease²⁰ may explain why the study of comorbidity in lung cancer patients has received scant attention. This view is extreme. Several studies have found that approximately 25–40% of predominantly stage I–III NSCLC patients died of competing causes without evidence of lung cancer recurrence or progression.^{21–24}

Only a few studies have investigated comorbidities in lung cancer patients, and they have looked at a limited number of comorbidities and at a small number of associations between comorbidities and other variables.^{25–28} Schrijvers *et al.*,²⁵ Janssen-Heijnen *et al.*,²⁶ Ogle *et al.*²⁷ and Lopez-Encuentra²⁸ evaluated cardiovascular disease (or myocardial infarction), hypertension, cerebrovascular disease, peripheral vascular disease, respiratory disease (or COPD), diabetes, previous cancers, selected other comorbidities pooled and arthritis (in 1 study). Battafarano *et al.*²⁹ investigated the survival impact of comorbidity in resected stage I NSCLC, but rather than report results for specific comorbidities, they used the Kaplan-Feinstein index as an aggregate measure of comorbidity. An extensive assessment of a broad range of comorbidities on lung cancer survival has not been made. Our purpose was to evaluate the effect of comorbidities individually and collectively on the survival of lung cancer patients and to determine to what extent existent effects are mediated through differences in receipt of cancer treatments. A more comprehensive range of comorbidities is considered than in previous studies, and the relative importance of comorbidity compared to established prognostic factors is estimated. Both advanced- and early-stage NSCLC and small cell lung cancer are assessed.

MATERIAL AND METHODS

A historical cohort study was carried out in the HFHS to evaluate the impact of comorbidity and other factors on lung cancer patient survival. Study subjects were identified through the JFCC Tumor Registry and had been diagnosed with primary bronchogenic lung cancer between 1 January 1995 and 31 December 1998 and received their principal care at the HFHS. The study was limited to blacks and whites as all other ethnic groups combined accounted for only 1% of lung cancer patients. Institutional review board approval was obtained.

Study data were collected from the JFCC Tumor Registry and systematically abstracted from computerized medical records. Initial assessment notes from all care providers, including pulmonologists, surgeons and radiation and medical oncologists, were reviewed; and all medical records were abstracted dating back to the patient's presenting symptoms or to the initial visit that ultimately led to diagnosis.

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HFHS, Henry Ford Health System; HR, hazard ratio; JFCC, Josephine Ford Cancer Center; NSCLC, non-small cell lung cancer; SES, socioeconomic status.

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mately led to a lung cancer diagnosis in asymptomatic patients. Records were abstracted until patient assessments in all relevant departments were complete, which usually occurred within 2–3 months of diagnosis. All abstraction was carried out by 1 of the authors (C.N.D.), an epidemiologist in the JFCC, or by 2 medical students under her supervision.

Data were collected on sociodemographic, exposure, clinicopathologic and treatment factors. Sociodemographic data included age, gender, ethnicity, marital status and SES. SES was estimated using block group median household income derived from the patient's address at diagnosis and 1990 U.S. census data. Exposure data included smoking history and alcohol, marijuana and illicit drug use. Clinicopathologic data incorporated comorbidity, tumor histopathology and stage; and treatment information covered receipt of surgery, chemotherapy and radiation therapy. Survival data were obtained through the JFCC Tumor Registry up until 1 January 2000 and included the date of death (all causes) or, for those not known to have died, the date of last contact (censoring date).

All comorbidities were abstracted and classified according to the Clinical Classification Software (previously known as the Clinical Classification for Health Policy Research), developed by the U.S. Department of Health and Human Services.^{30,31} This system collapses over 12,000 diseases in the *International Classification of Diseases, 9th Revision, Clinical Modifications*³² into 259 clinically and biologically homogeneous groups. Fifty-six categories of comorbidity were considered (Tables I, II).

The total number of comorbid conditions per individual was evaluated and is referred to as the *comorbidity count*. Reproductive tract comorbidities were not included in comorbidity counts, to ensure intergender comparability. In preparing comorbidity counts, double counting of overlapping categories was avoided. Exposure factors were not incorporated into comorbidity counts, to allow analysis of their relationship with comorbidity as they may lie in the causal pathway leading to certain comorbidities. The Charlson index of comorbidity³³ was computed for comparative purposes. This summary method produces an individual score by tallying together the weighted score of 19 comorbidities. The weights range from 1 to 6 (0 if the comorbidity is absent) and were originally based on the 1-year mortality patterns of a cohort of hospitalized patients.

In modeling, AJCC TNM stage³⁴ groups were treated as categorical variables with 5 levels (I–IV and unstaged). Six lung cancer histotypes based on the WHO histologic classification system³⁵ were coded into the following classes: adenocarcinoma, bronchioloalveolar, squamous cell and small cell carcinomas; other defined histotypes pooled (including large cell and mixed types); and bronchogenic carcinoma not otherwise specified. Cancer treatment data were taken from the JFCC Tumor Registry and analyzed as 3 dichotomous variables: surgery, chemotherapy and radiation therapy (each administered or not administered).

Statistical methods

The effect of predictor variables on survival was evaluated at the univariate level using the product-limit life-table method, Kaplan-Meier survival plots³⁶ and log-rank tests³⁷ and at multivariate levels using HRs and associated 95% CIs prepared by Cox proportional hazards regression modeling.³⁸ Cox model HRs and 95% CIs were also prepared using bootstrapping with 1,000 resamples per model,³⁹ and these estimates were compared to those obtained by traditional Cox modeling methods.

Modeling of comorbidity hazard was carried out as follows. The HR for each of the 56 comorbidities was evaluated in univariate Cox models as well as in models adjusted for recognized prognostic factors (baseline covariates), which include age, gender, smoking status, histology and stage. All comorbidities that displayed HRs of 1.20 or greater in any of these models were further evaluated in models adjusted for other important comorbidities, cancer treatments and both. These adjustments allowed evaluation

of the amount of hazard for a given comorbidity that is attributable to baseline covariates, associated comorbidities and differences in receipt of treatments. For a significant predictive comorbidity, an HR change of $\geq 15\%$ in magnitude following adjustment was considered to be important.^{40–42}

Smoking status (current vs. former and never smoker) was included in the baseline covariate set because in this study population and in previous studies^{24,43,44} smoking was an independent and significant predictor of shortened survival. Race, SES and marital status were not included in the baseline covariate set. Although they were found to be significant univariate predictors of survival, their effects approached the null following adjustment for baseline covariates.

The adjusted R^2 statistic was used to describe the proportion of survival variation explained by predictor variables in Cox proportional hazards models.^{45,46} In linear regression, the R^2 statistic describes the amount of variance in the dependent variable that is explained by the predictor variable(s). Although not completely analogous, the same equation used to calculate R^2 in linear regression [$R^2 = 1 - \exp(-G^2/n)$, where G^2 is the likelihood ratio χ^2 statistic] can be applied to Cox models in survival analysis.^{45,46} The use of R^2 to evaluate goodness of fit has been criticized,^{47–49} but these criticisms do not apply to the use of R^2 as a measure of explained risk.^{50–52} Adjusted R^2 values, which compensate for the number of predictor variables, are presented here.

To ensure reliability of record abstraction, 5% of records were reabstracted blind to the results of the initial abstraction and concordance was estimated by calculating percent agreement. Thirty different comorbidities occurred in these 60 patient records, and for 29 of them the abstract–reabstract agreements were $>90\%$. The lowest agreement observed for any variable was 86%. These findings indicate that data were abstracted reliably.

SAS 6.12 (SAS Institute, Cary, NC), S-Plus 6 (Insightful, Seattle, WA) and Stata 7.0 (Stata, College Station, TX) software were used to prepare statistics and figures. All reported p values are 2-sided.

RESULTS

Details of the study population characteristics and of the distributions and associations of comorbidities are presented elsewhere (unpublished). The median follow-up of those not dying was 819 days. During the follow-up period, 841 deaths were observed (72.8% of the population) and the median survival was 0.86 years (95% CI 0.79–0.95).

Univariate Cox models indicate that age (HR_{per year} = 1.01, 95% CI 1.01–1.02, $p = 0.0001$), ethnicity (HR_{black vs. white} = 1.20, 95% CI 1.05–1.38, $p = 0.008$), SES (HR_{per \$10,000} = 0.92, 95% CI 0.89–0.96, $p = 0.0001$), marital status (HR_{not vs. married} = 1.27, 95% CI 1.11–1.45, $p = 0.0007$) and smoking status (HR_{current vs. former/never smoker} = 1.29, 95% CI 1.12–1.48, $p = 0.0004$) were significant predictors of survival. Stage and histologic type were modeled as multiple indicator variables, and both collectively were significant ($p < 0.0001$ and $p = 0.01$, respectively). Adjusted for the baseline covariates (age, gender, smoking status, histology and stage), the HRs for race, SES and marital status approached the null, indicating that they were not independent predictors of survival. Adjusted for the baseline covariates and each other, the HR for surgery was 0.54 (95% CI 0.42–0.69, $p = 0.0001$), that for chemotherapy was 0.45 (95% CI 0.39–0.53, $p = 0.0001$) and that for radiation therapy was 0.98 (95% CI 0.85–1.13, $p = 0.81$).

In Cox models, adjusted for the baseline covariates, for baseline covariates and other comorbidities or for baseline covariates, other comorbidities and treatments, 19 comorbidities were important predictors of survival in lung cancer patients (Table I): HIV/AIDS, tuberculosis (active or current cases), previous metastatic cancer, thyroid/glandular disorder (excluding diabetes mellitus), electrolyte/mineral imbalance, anemia (pretreatment), other blood dis-

TABLE 1—COX MODEL HRS (95% CI, *P* VALUE) FOR COMORBIDITIES ADJUSTED FOR BASELINE COVARIATES AND FURTHER ADJUSTED FOR TREATMENTS, FOR OTHER COMORBIDITIES AND FOR TREATMENTS AND OTHER COMORBIDITIES

	Prevalence	A: Models include 1 comorbidity at a time adjusted for baseline covariates	B: Models include 2 comorbidity at a time adjusted for baseline covariates and treatments	C: Model includes baseline covariates and all comorbidities	D: Model includes baseline covariates, all comorbidities and treatments
Baseline covariates					
Age (per 1 year)		Included	Included	1.03 (1.02–1.04, <i>p</i> = 0.0001)	1.02 (1.01–1.03, <i>p</i> = 0.0001)
Gender (Male vs. female)	59.3%	Included	Included	1.23 (1.05–1.43, <i>p</i> = 0.01)	1.23 (1.06–1.44, <i>p</i> = 0.008)
Smoking (current vs. former and never)	47.9%	Included	Included	1.38 (1.19–1.60, <i>p</i> = 0.0001)	1.35 (1.17–1.56, <i>p</i> = 0.0001)
Histologic type (6 levels)		Included	Included	Included	Included
Stage (5 levels)		Included	Included	Included	Included
Treatments					
Surgery	17.7%	Excluded	Included	Excluded	0.52 (0.41–0.67, <i>p</i> = 0.0001)
Chemotherapy	43.1%	Excluded	Included	Excluded	0.48 (0.41–0.57, <i>p</i> = 0.0001)
Radiation therapy	42.8%	Excluded	Included	Excluded	0.99 (0.85–1.14, <i>p</i> = 0.86)
Comorbidities					
HIV/AIDS	0.7%	4.77 (2.33–9.76, <i>p</i> = 0.0001)	4.61 (2.25–9.41, <i>p</i> = 0.0001)	3.69 (1.72–7.93, <i>p</i> = 0.0008)	3.76 (1.77–7.99, <i>p</i> = 0.0006)
Tuberculosis	0.4%	3.63 (0.90–14.72, <i>p</i> = 0.07)	4.73 (1.16–19.25, <i>p</i> = 0.03)	3.45 (0.84–14.09, <i>p</i> = 0.09)	4.47 (1.09–18.36, <i>p</i> = 0.04)
Previous metastatic cancer	1.2%	1.61 (0.91–2.87, <i>p</i> = 0.10)	2.10 (1.18–3.75, <i>p</i> = 0.01)	1.90 (1.07–3.40, <i>p</i> = 0.03)	2.44 (1.36–4.37, <i>p</i> = 0.003)
Thyroid/glandular	7.2%	1.35 (1.03–1.77, <i>p</i> = 0.03)	1.33 (1.01–1.75, <i>p</i> = 0.04)	1.26 (0.95–1.69, <i>p</i> = 0.11)	1.27 (0.95–1.69, <i>p</i> = 0.11)
Electrolyte/mineral imbalance	1.1%	2.21 (1.24–3.96, <i>p</i> = 0.007)	2.05 (1.15–3.68, <i>p</i> = 0.02)	1.98 (1.08–3.61, <i>p</i> = 0.03)	1.81 (0.99–3.30, <i>p</i> = 0.05)
Anemia	6.7%	1.34 (1.03–1.75, <i>p</i> = 0.03)	1.24 (0.95–1.63, <i>p</i> = 0.11)	1.19 (0.90–1.58, <i>p</i> = 0.21)	1.13 (0.85–1.49, <i>p</i> = 0.40)
Blood disorder	0.8%	5.30 (2.62–10.73, <i>p</i> = 0.0001)	4.55 (2.22–9.30, <i>p</i> = 0.0001)	3.75 (1.73–8.13, <i>p</i> = 0.0008)	3.53 (1.61–7.72, <i>p</i> = 0.002)
Dementia	2.0%	2.01 (1.20–3.38, <i>p</i> = 0.008)	1.61 (0.96–2.69, <i>p</i> = 0.07)	1.30 (0.73–2.29, <i>p</i> = 0.37)	1.10 (0.63–1.93, <i>p</i> = 0.74)
Neurologic disease	1.6%	2.05 (1.25–3.37, <i>p</i> = 0.005)	1.93 (1.18–3.16, <i>p</i> = 0.009)	2.35 (1.40–3.96, <i>p</i> = 0.001)	2.23 (1.35–3.68, <i>p</i> = 0.002)
Congestive heart failure	7.6%	1.46 (1.15–1.86, <i>p</i> = 0.002)	1.23 (0.97–1.58, <i>p</i> = 0.09)	1.45 (1.13–1.85, <i>p</i> = 0.004)	1.24 (0.96–1.59, <i>p</i> = 0.10)
COPD	28.6%	1.32 (1.13–1.55, <i>p</i> = 0.0005)	1.22 (1.04–1.43, <i>p</i> = 0.02)	1.31 (1.11–1.55, <i>p</i> = 0.001)	1.23 (1.04–1.45, <i>p</i> = 0.01)
Asthma	4.4%	1.45 (1.03–2.03, <i>p</i> = 0.03)	1.43 (1.02–2.02, <i>p</i> = 0.04)	1.46 (1.03–2.06, <i>p</i> = 0.03)	1.46 (1.03–2.07, <i>p</i> = 0.03)
Pulmonary fibrosis	0.5%	3.59 (1.31–9.88, <i>p</i> = 0.01)	3.46 (1.26–9.49, <i>p</i> = 0.02)	4.38 (1.59–12.10, <i>p</i> = 0.004)	4.12 (1.49–11.40, <i>p</i> = 0.006)
Liver disease	2.8%	1.82 (1.22–2.71, <i>p</i> = 0.003)	1.62 (1.09–2.41, <i>p</i> = 0.02)	1.38 (0.91–2.11, <i>p</i> = 0.13)	1.23 (0.81–1.87, <i>p</i> = 0.34)
Gastrointestinal bleeding	1.4%	2.54 (1.48–4.36, <i>p</i> = 0.0007)	2.69 (1.57–4.60, <i>p</i> = 0.0003)	2.12 (1.21–3.73, <i>p</i> = 0.009)	2.30 (1.32–4.01, <i>p</i> = 0.003)
Renal disease	5.9%	1.53 (1.16–2.00, <i>p</i> = 0.002)	1.33 (1.01–1.75, <i>p</i> = 0.04)	1.41 (1.05–1.89, <i>p</i> = 0.02)	1.28 (0.95–1.72, <i>p</i> = 0.10)
Connective tissue disease	22.2%	1.31 (1.11–1.54, <i>p</i> = 0.001)	1.27 (1.08–1.49, <i>p</i> = 0.005)	1.26 (1.07–1.49, <i>p</i> = 0.006)	1.23 (1.04–1.46, <i>p</i> = 0.01)
Osteoporosis	2.2%	1.59 (1.03–2.47, <i>p</i> = 0.04)	1.82 (1.17–2.84, <i>p</i> = 0.008)	1.60 (1.02–2.50, <i>p</i> = 0.04)	1.81 (1.15–2.84, <i>p</i> = 0.01)
Peripheral vascular disease	10.2%	0.83 (0.66–1.05, <i>p</i> = 0.13)	0.82 (0.65–1.03, <i>p</i> = 0.09)	0.75 (0.59–0.95, <i>p</i> = 0.02)	0.75 (0.59–0.95, <i>p</i> = 0.02)

TABLE II – COMORBIDITIES GROUPED BY SURVIVAL EFFECTS IN ADJUSTED COX MODELS.¹ SELECTED HRS, 95% CIs AND *P* VALUES ARE PRESENTED

Survival effect	Comorbidity
Elevated adjusted HR but imprecise CIs prevents drawing conclusions	1. Diabetes with end-organ damage (1.40, 95% CI 0.2–2.72, <i>p</i> = 0.33) 2. Severe obesity/malnutrition (1.91, 95% CI 0.78–4.68, <i>p</i> = 0.15) 3. Immunologic disorder (1.47, 95% CI 0.65–3.29, <i>p</i> = 0.35) 4. Eye/ophthalmic disease (1.20, 95% CI 0.95–1.50, <i>p</i> = 0.12) 5. Heart valve disease (1.54, 95% CI 0.84–2.81, <i>p</i> = 0.16) 6. Plegia (1.48, 95% CI 0.76–2.88, <i>p</i> = 0.25) 7. Pneumonia, ≥ 2 adult episodes (1.32, 95% CI 0.91–1.90, <i>p</i> = 0.14) 8. Hepatitis (1.25, 95% CI 0.68–2.29, <i>p</i> = 0.47) 9. Other digestive system disease (1.21, 95% CI 0.78–1.89, <i>p</i> = 0.39) 10. Urinary tract disease (nonrenal) (1.29, 95% CI 0.64–2.63, <i>p</i> = 0.48)
Magnitude of adjusted HR does not suggest a strong survival effect	11. Syphilis and other sexually transmitted diseases 12. Other serious adult infections 13. Previous cancer without metastasis 14. Diabetes mellitus, no end-organ damage 15. Lipid problem/hypercholesterolemia 16. Psychiatric disorder 17. Seizure/convulsion 18. Hypertension 19. Coronary artery disease 20. Myocardial infarction 21. Angina 22. Arrhythmia (dysrhythmia) ² 23. Cardiac arrest 24. Aneurysm 25. Cerebrovascular disease 26. Other cardiovascular diseases 27. Emphysema 28. Chronic bronchitis 29. Other respiratory disease 30. Esophageal disease 31. Gastroesophageal reflux disease ² 32. Gastroduodenal ulcers 33. Gallbladder disease 34. Pancreatic disease 35. Diverticulosis 36. Gastrointestinal polyps 37. Adult fracture

¹Cox models were adjusted for age, gender, smoking status, histology and stage. ²Arrhythmia demonstrated an elevated univariate hazard that was primarily explained by association with advanced age. Gastroesophageal reflux disease demonstrated a univariate protective effect primarily due to association with earlier stage at diagnosis.

TABLE III – MEDIAN SURVIVAL AND UNIVARIATE HRS FOR 19 PREDICTIVE COMORBIDITIES

Comorbidity	Median survival (years)	HR (95% CI, <i>p</i> value)
HIV/AIDS	0.40	2.33 (1.16–4.67, <i>p</i> = 0.02)
Tuberculosis	0.42	2.23 (0.92–5.37, <i>p</i> = 0.07)
Previous metastatic cancer	0.68	1.30 (0.74–2.31, <i>p</i> = 0.36)
Thyroid/glandular	0.68	1.17 (0.91–1.52, <i>p</i> = 0.22)
Electrolyte/mineral imbalance	0.42	1.83 (1.06–3.17, <i>p</i> = 0.03)
Anemia	0.51	1.53 (1.193–1.96, <i>p</i> = 0.001)
Blood disorder	0.15	3.06 (1.59–5.92, <i>p</i> = 0.001)
Dementia	0.12	3.42 (2.24–5.23, <i>p</i> < 0.0001)
Neurologic disease	0.47	2.24 (1.40–3.57, <i>p</i> = 0.001)
Congestive heart failure	0.60	1.52 (1.21–1.92, <i>p</i> < 0.001)
COPD	0.85	1.15 (0.99–1.33, <i>p</i> = 0.06)
Asthma	0.90	1.08 (0.78–1.51, <i>p</i> = 0.64)
Pulmonary fibrosis	0.29	2.67 (1.19–5.96, <i>p</i> = 0.02)
Liver disease	0.64	1.30 (0.89–1.91, <i>p</i> = 0.18)
Gastrointestinal bleeding	0.37	2.03 (1.19–3.44, <i>p</i> = 0.009)
Renal disease	0.45	1.67 (1.29–2.17, <i>p</i> < 0.001)
Connective tissue disease	0.65	1.30 (1.11–1.52, <i>p</i> = 0.001)
Osteoporosis	0.62	1.45 (0.94–2.23, <i>p</i> = 0.09)
Peripheral vascular disease	1.08	1.00 (0.80–1.25, <i>p</i> = 0.98)

eases (not primary anemia), dementia, neurologic disease, congestive heart failure, COPD, asthma, pulmonary fibrosis/interstitial disease, liver disease, gastrointestinal bleeding, renal disease, connective tissue/musculoskeletal disease, osteoporosis and peripheral vascular disease. All but peripheral vascular disease predicted

shortened survival. Univariate HRs for these 19 predictive comorbidities are presented in Table III, and Kaplan-Meier survival plots for select predictive comorbidities are presented in Figure 1. For asthma, peripheral vascular disease and previous metastatic cancer, the Kaplan-Meier survival plots, which are univariate unad-

justed depictions, were unrepresentative of the survival patterns unveiled in adjusted analysis and are not presented.

In adjusted models, 10 of the 56 comorbidities under study had elevated HR point estimates ($HR \geq 1.20$), suggestive of hazardous effects; however, CIs included the null, and firm conclusions were not drawn (Table II). Twenty-seven comorbidities had adjusted HR estimates, suggesting no strong survival effect ($HR < 1.20$, $p > 0.10$) (Table II).

In Table I, column A presents HRs for comorbidities adjusted for the baseline covariates and provides a sense of the hazard associated with each comorbidity independent of age, gender, smoking status, histology and stage. In Table I, column B presents the HRs for individual comorbidities adjusted for the baseline covariates as well as receipt of treatments (surgery, chemotherapy and radiation therapy), and the difference between estimates in columns A and B provides a sense of how much of the comorbidity hazard is associated with nonreceipt of cancer treatments. In Table I, column C presents HRs for comorbidities adjusted for baseline covariates and other prognostic comorbidities (*i.e.*, other comorbidities in column C). The difference in estimates between columns A and C for a given comorbidity represents the amount of hazard explained by other comorbidities in the model. Based on Cox model adjustment, the hazardous effects of asthma, tuberculosis, previous metastatic cancer, osteoporosis, pulmonary fibrosis/interstitial disease and neurologic disease were relatively direct in that they were not mediated by other comorbidities and treatments (Fig. 2, lower left cluster). The hazards associated with congestive heart failure and COPD were not explained by other comorbidities but were explained to a considerable extent by nonreceipt of treatments (Fig. 2, left, upper cluster). The hazards for HIV/AIDS, gastrointestinal bleeding, thyroid/glandular disease, electrolyte/mineral imbalance and connective tissue/musculoskeletal disease were not explained by treatments; but moderate amounts of their hazards (15–30%) were explained by their associations with other comorbidities (Fig. 2, right, lower cluster). Important amounts (>15%) of hazard associated with dementia, anemia and liver, blood and renal diseases were explained by nonreceipt of treatments and by their associations with other comorbidities. For the former 3 comorbidities, the majority of the hazard was explained by other comorbidities (Fig. 2, right, upper cluster).

Bootstrap estimates for HRs and 95% CIs for the 19 predictive comorbidities adjusted for baseline covariates were prepared. Bootstrap estimates of effect size and CIs are unbiased by distributional idiosyncrasies and, thus, can be more valid than those produced by parametric models and can point to weaknesses in the estimates presented here. Estimates were obtained for 18 of 19 comorbidities. Because of the small number of cases, no bootstrap estimate was obtained for pulmonary fibrosis/interstitial lung disease. For the remaining 18 comorbidities, bootstrap HR point estimates confirmed those obtained by standard Cox methods and bootstrap 95% CIs confirmed the non-null baseline covariate-adjusted HRs for all comorbidities except dementia and asthma. The bootstrap HR estimate for dementia was 2.30 (95% CI 0.88–3.71). The CI includes the null. Bootstrap estimates confirmed the important non-null univariate effect of dementia ($HR = 3.74$, 95% CI 2.17–5.42). A large amount of the univariate effect of dementia was mediated through baseline covariates. The bootstrap HR estimate for asthma was 1.47 (95% CI 0.92–1.99). The CIs included the null value, indicating that less confidence should be placed in the hazard estimate than was indicated by the Cox model estimate.

Survival of early-stage lung cancer is much better than that of advanced disease, and it is possible that the impact of comorbidity is limited to, or predominates in, early-stage disease. To assess this possibility, the impacts of predictive comorbidities were assessed stratified by early-stage (I, II) vs. advanced-stage (III, IV and unstaged). The results are presented in Table IV. For the 18 deleterious comorbidities, HR estimates consistently predict shortened survival in both early and advanced stages, with the exception of tuberculosis, for which there were no early-stage cases. Al-

though the magnitude of the hazard was larger in early-stage disease for 16 of 17 deleterious comorbidities for which comparisons were possible, for 14 specific comparisons CIs overlapped. Although the HR CIs for dementia in early stage did not overlap those for advanced stage, the estimate in early stage is imprecise and unreliable. The nonoverlapping 95% CIs for liver disease in early and advanced stage suggest that liver disease may have a greater impact on survival in individuals with early-stage disease. In the adjusted Cox model, the interaction term between stage and liver disease was significant ($p = 0.03$). Nevertheless, despite the sample sizes being reduced by stratification, in advanced-stage disease 10 of 18 deleterious comorbidities had HRs that were significantly elevated and an additional 4 comorbidities demonstrated trends to significance ($0.05 < p \leq 0.15$). Adjusted for age, gender, smoking and histology, the HR for 1 or more deleterious comorbidity in early-stage disease was 2.18 (95% CI 1.43–3.32, $p < 0.001$) and that in late-stage disease was 1.54 (95% CI 1.31–1.80, $p < 0.001$) (Fig. 3).

Comorbidity count, a simple aggregate measure of comorbidity, was a highly significant predictor of survival. In univariate analysis, comorbidity count had an HR of 1.06 (95% CI 1.03–1.10, $p = 0.0001$) per one level increase (Fig. 4). Adjusted for baseline covariates, comorbidity count had an HR of 1.082 (95% CI 1.05–1.12, $p = 0.0001$), and the Charlson index had an HR of 1.083 (95% CI 1.05–1.12, $p = 0.0001$). Adjusted for the baseline covariates, the HR for comorbidity counts divided into roughly equally sized groups of 1–2, 3–4 and >4 comorbidities compared to 0 comorbidities demonstrated a dose-response: 1.37 (95% CI 1.07–1.75, $p = 0.01$), 1.44 (95% CI 1.12–1.86, $p = 0.004$) and 2.04 (95% CI 1.57–2.66, $p = 0.0001$), respectively. Adjusted for baseline covariates and cancer treatments, comorbidity count had an HR of 1.061 (95% CI 1.03–1.10, $p = 0.0005$) and the Charlson index had an HR of 1.059 (95% CI 1.02–1.10, $p = 0.001$). A substantial amount of the hazard for comorbidity count and for the Charlson index was explained by receipt of treatments (25.6% and 28.9%, respectively). However, even after adjustment for treatments, comorbidity count and the Charlson index remained independent significant predictors of survival.

Differences in the adjusted R^2 statistic were used to compare the explanatory ability of comorbidity relative to other predictors. Stage was by far the most important predictor of survival with an adjusted R^2 of 25.4%, while the complete model including the baseline covariates, 19 predictive comorbidities and the 3 treatments had an adjusted R^2 of 42.3%. In addition to stage, the 3 treatments in aggregate explained 9.2% of the survival variation and the 19 predictive comorbidities collectively explained 6.1%. In addition to stage, the dichotomous variable, having 1 or more of the 18 deleterious comorbidities vs. none, which is a crude simple measure, had an adjusted R^2 of 3.9%. In contrast, in addition to stage, the adjusted R^2 values were 3.7% for age, 1.3% for histology, 0.8% for smoking and 0.3% for gender; in aggregate, these 4 variables explained 6.0% of the survival variation. In addition to stage, comorbidity count and the Charlson index explained 2.5% and 2.0% of the survival variation, respectively.

DISCUSSION

We found that comorbidity in general (comorbidity count) and 18 specific comorbidities were associated with reduced lung cancer survival. Generally, effects were apparent in both early and late stages, though they tended to be of greater magnitude in early-stage disease. Gijzen *et al.*⁵³ reviewed the causes and consequences of comorbidity. They generalized that “comorbidity was not independently associated with mortality in situations in which (a) the index-disease was especially lethal and (b) when the explanatory model included a number of clinical variables associated with the index-diseases”. Our findings do not support either of these conclusions. Lung cancer is one of the most aggressive of cancers, and we found 19 comorbidities to independently predict

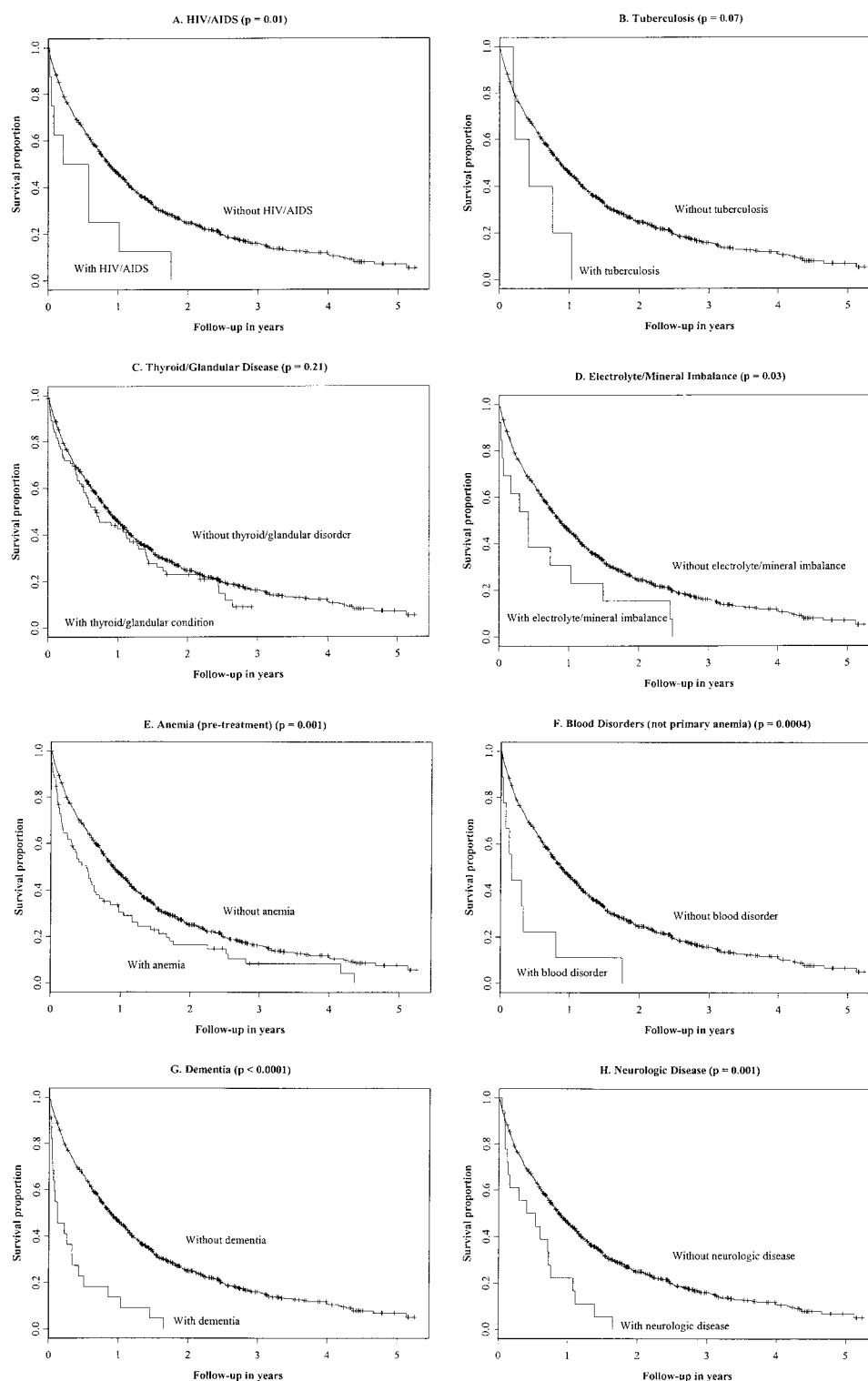


FIGURE 1 – Kaplan-Meier survival plots for 1,155 lung cancer patients stratified by select prognostic comorbidities (log rank test p values).

survival, with careful adjustment for 2 of the most important clinical variables, histology and stage.

To date, the survival effects of the 19 predictive comorbidities have been studied to a limited extent. Caro *et al.*⁵⁴ reviewed the prognostic effect of anemia in cancer patients and concluded that it was an independent predictor of survival in lung and other cancer patients. They did not investigate whether this effect was in

part mediated through other comorbid conditions and treatments, as was indicated in our study. The injurious effects of most of the comorbidities found to impact lung cancer survival in our study make clinical sense because they, directly or through their association with other comorbidities, diminish the function of vital organs or systems and may compromise treatment. One enigma is osteoporosis, generally a nonlethal disease, which demonstrated an

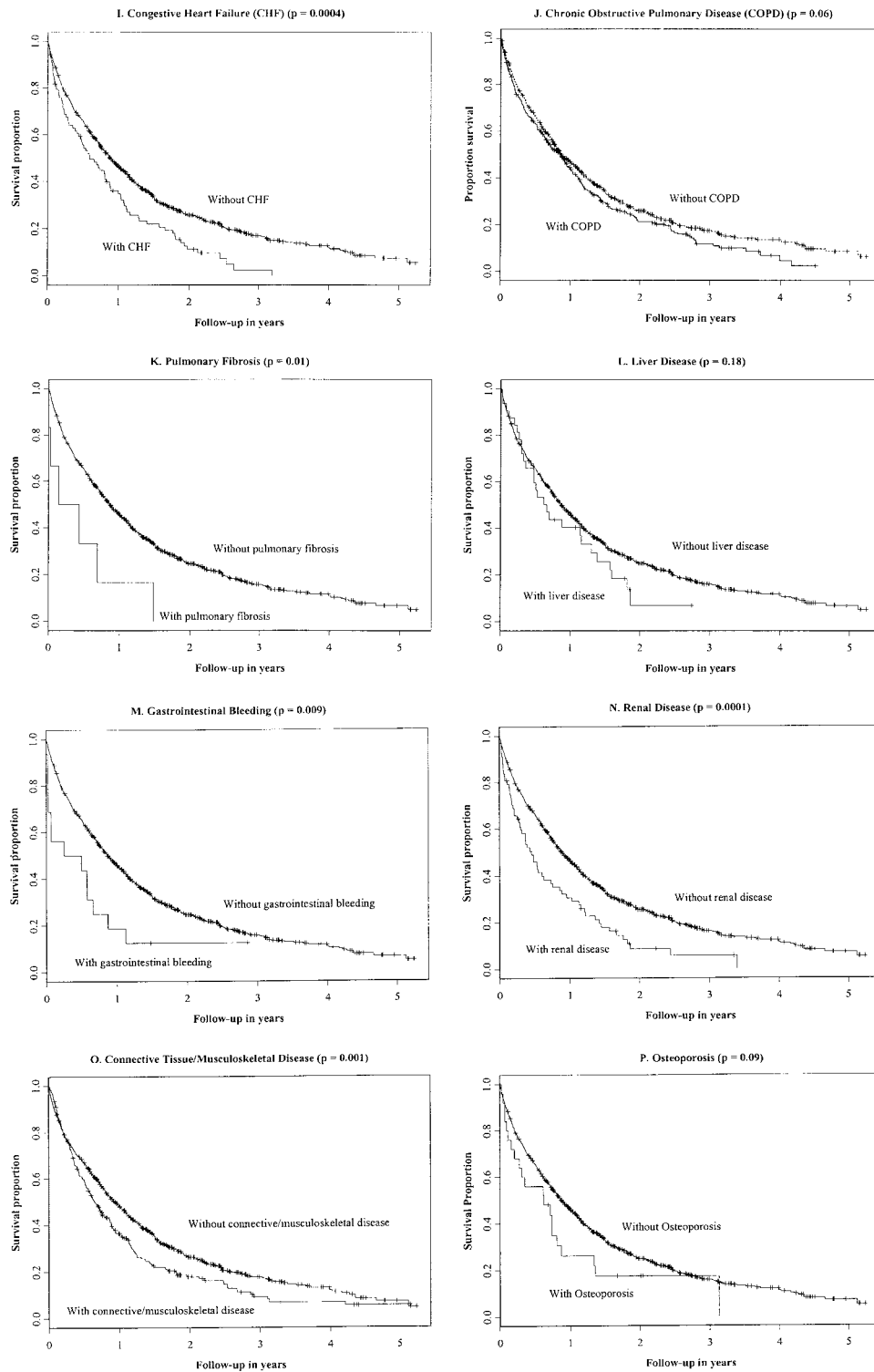


FIGURE 1 – Continued

important independent effect on survival. Peripheral vascular disease was associated with improved survival. Some research indicates that anticoagulants, which are used in the treatment of peripheral vascular disease, inhibit cancer progression and metastasis;^{55,56} but it is not known whether anticoagulant treatment explains the protective effect observed for peripheral vascular disease in the present study.

Several adverse comorbidities that individually were uncommon ($\leq 6\%$) and that have been overlooked in past studies of comorbidity, collectively were relatively common and important in lung cancer patients. They included HIV/AIDS, tuberculosis, previous metastatic cancer, electrolyte/mineral imbalance, blood disorder, dementia, neurologic disease, pulmonary fibrosis/interstitial disease, asthma, liver disease, gastrointestinal bleeding, renal disease

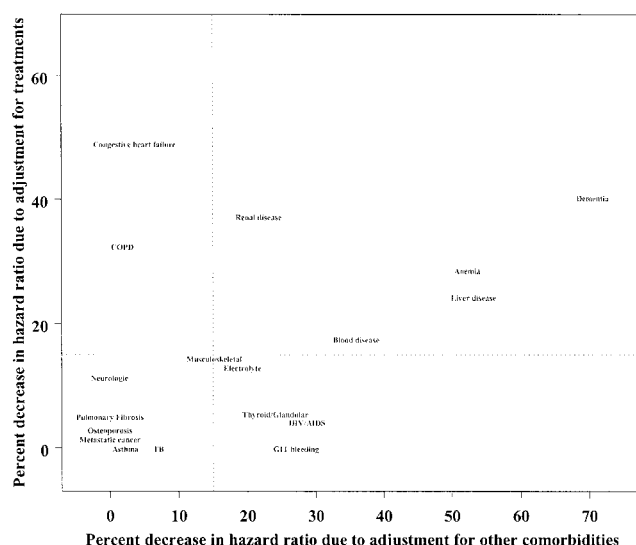


FIGURE 2 – Percent decrease in adjusted HRs (adjusted for baseline covariate: age, gender, smoking status, histology and stage) for prognostic comorbidities further adjusted for other prognostic comorbidities (listed in Table II) or for cancer treatments (adjusted for treatment entered into models as 3 dichotomous variables: surgery, chemotherapy and radiation therapy).

and osteoporosis. One or more of these 13 infrequent comorbidities was present in 21.2% of patients, and collectively in addition to stage they explained 3.5% (adjusted R^2) of the survival variation, more than was explained by histology, comorbidity count or the Charlson index. Thus, the study of comorbidity, at least in lung cancer patients, should not be restricted to a limited number of major comorbidities.

Our findings suggest that existing comorbidity indexes may be suboptimal for application in lung cancer patients because they include unimportant comorbidities, exclude important comorbidities and apply weightings to comorbidities that do not reflect true hazards. Summarizing a multidimensional phenomenon such as comorbidity is not an easy matter, and currently no standard method exists for assessing comorbidities collectively. However, summary comorbidity indexes are desirable for several reasons. They can simplify complex data for clinical and research purposes and enable comparisons across populations and diseases. The simplest approach to summarizing comorbidity data is to tally together patient's comorbidities. Although such a comorbidity count has been found to correlate strongly with disability and functional well-being,⁵⁷ this method suffers from weaknesses. Different studies may tally together different categories and numbers of comorbidities, and comorbidity count does not weight the comorbidities by their relative hazards and disease severity. Several indexes have attempted to overcome some or all of these problems and have been validated by demonstration of reliability and by significantly predicting medical outcomes.^{19,58} For example, the Kaplan-Feinstein index⁵⁹ has been used in studies of breast,^{33,60} prostate,^{16,61,62} head-and-neck^{17,63} and lung²⁹ cancers. The Index of Coexistent Disease has been used in studies of breast^{9,64} and prostate^{14,65} cancers. The Charlson index has been used in the study of breast,^{10,11,33,60,66} prostate⁶⁷ and head-and-neck¹⁶ cancers, as well as multiple cancer types.⁶⁸ The method described by Havlik and Yancik has been employed in the study of breast¹² and colorectal¹⁵ cancers as well as multiple cancer types collectively.^{6,69,70} The Cumulative Illness Rating Scale^{71,72} has been used to study multiple cancer types collectively.⁶⁸ None of these indexes was developed or validated in lung cancer patients.

In applying existing comorbidity indexes to studies of lung cancer, several issues need to be considered. Comorbidity in lung cancer patients may differ in important ways from comorbidity in other cancer patients. Lung cancer is strongly associated with smoking, a major cause of comorbidity. Hence, the diversity and count of comorbidities may be greater in lung cancer patients.¹⁸ Lung cancer has a relatively short course, and indolent comorbidities may not have the opportunity to exert deleterious effects. The respiratory tract of lung cancer patients is compromised by the cancer, and additional pulmonary comorbidities may not be tolerated as well as by patients free of tumors in their lungs. Thus, the comorbidity indexes that were developed and validated in non-lung cancer patients may not perform well in lung cancer patients. The findings of the current study support this view. For example, hypertension, coronary artery disease, myocardial infarct, cerebrovascular disease and diabetes, perceived to be of major importance in other studies^{25–27} or in established comorbidity indexes,^{15,33,73,74} were not found to be important predictors of survival in lung cancer patients.

Moreover, the current study indicates that even if an index is significantly predictive of a health outcome and does so in a dose-response fashion, it may be far from optimal. In multivariate Cox models, comorbidities were evaluated using 3 approaches: comorbidity count, the Charlson index and inclusion of specific relevant comorbidities. All 3 approaches found comorbidity to be highly significant. In Cox models after inclusion of stage, the adjusted R^2 for comorbidity count was 2.5%, that for the Charlson index was 2.0% and that for the collective group of 19 predictive comorbidities was 6.1%. These adjusted R^2 values suggest that the amount of survival data that can potentially be explained by comorbidity is higher than that found by comorbidity count or the Charlson index. This comparison may not be entirely fair. In this analysis, the Charlson index was evaluated in a test sample, whereas the 19 predictive comorbidities were evaluated in the same sample in which they were trained and fitted to random and site-specific sampling variation. It is unlikely that the 19 predictive comorbidities will explain as much survival variation in a test sample. Nevertheless, the Charlson index failed to outperform the simplest of indexes, the comorbidity count, and it is unlikely that the 3-fold spread in adjusted R^2 values between the Charlson index and the 19 comorbidities in aggregate can be explained by overfit of the model.

Battafarano *et al.*²⁹ evaluated the impact of comorbidity, measured by a modified Kaplan-Feinstein index, on the survival of surgically resected stage I NSCLC patients. Although they found both moderate and severe comorbidity scores to be associated with significant hazard, those with moderate scores were at 36% greater risk than those with severe scores. A good prognostic comorbidity index should have a graded relationship with hazard; in the current study, even the crudest index, the comorbidity count, demonstrated a monotonic dose-response.

Thus, it appears that a lung cancer-specific comorbidity index based on empirical data may be valuable. Such an index may not allow comparisons across different diseases but might be much better suited for widespread application in lung cancer, and a great deal of clinical and research application does not require the universal applicability of indexes across disease types.

Our study demonstrates that while some comorbidities have a relatively direct impact on survival (asthma, tuberculosis, previous metastatic cancer, osteoporosis, pulmonary fibrosis/interstitial disease and neurologic disease), some comorbidities are associated with shorter survival because of their association with other comorbidities (HIV/AIDS, gastrointestinal bleeding, thyroid/glandular disorder, electrolyte/mineral imbalance and connective tissue/musculoskeletal disease) or because of nonreceipt of cancer treatment (congestive heart failure and COPD) or their association with other comorbidities and nonreceipt of treatments (dementia, anemia and liver, renal and other blood diseases). This highlights one limitation of comorbidity indexes: they do not allow the study

TABLE IV – ADJUSTED¹ HRS AND PREVALENCE OF PREDICTIVE COMORBIDITIES STRATIFIED BY EARLY AND ADVANCED STAGE

Comorbidity	HR (95% CI, <i>p</i> value)		Prevalence (%)		
	Stage I, II	Stage III, IV and unstaged	Stage I, II	Stage III, IV and unstaged	<i>p</i> value ²
HIV/AIDS	8.49 (1.02–70.39, <i>p</i> = 0.05)	3.31 (1.55–7.07, <i>p</i> = 0.002)	0.3	0.8	0.69
Tuberculosis	Not applicable	3.31 (0.81–13.42, <i>p</i> = 0.09)	0.0	0.6	0.33
Previous metastatic cancer	2.62 (1.05–6.52, <i>p</i> = 0.04)	1.50 (0.71–3.17, <i>p</i> = 0.29)	2.3	0.8	0.06
Thyroid/glandular	1.19 (0.58–2.46, <i>p</i> = 0.64)	1.37 (1.02–1.84, <i>p</i> = 0.03)	7.5	7.1	0.80
Electrolyte/mineral imbalance	4.32 (1.29–14.47, <i>p</i> = 0.02)	1.73 (0.89–3.37, <i>p</i> = 0.11)	1.0	1.2	1.00
Anemia	3.02 (1.46–6.25, <i>p</i> = 0.003)	1.16 (0.87–1.55, <i>p</i> = 0.30)	3.9	7.8	0.02
Blood disorder	9.37 (2.77–31.69, <i>p</i> = 0.0003)	5.97 (2.45–14.54, <i>p</i> = 0.0001)	0.7	0.8	0.71
Dementia	44.69 (5.00–400.31, <i>p</i> = 0.001)	2.01 (1.18–3.43, <i>p</i> = 0.01)	0.3	2.6	0.01
Neurologic disease	3.39 (1.03–11.19, <i>p</i> = 0.04)	1.90 (1.10–3.27, <i>p</i> = 0.02)	1.0	1.8	0.43
Congestive heart failure	1.53 (0.78–3.02, <i>p</i> = 0.22)	1.35 (1.04–1.76, <i>p</i> = 0.03)	5.6	8.4	0.13
COPD	1.44 (1.01–2.06, <i>p</i> = 0.04)	1.21 (1.01–1.44, <i>p</i> = 0.03)	36.6	25.7	<0.001
Asthma	2.30 (1.22–4.33, <i>p</i> = 0.01)	1.35 (0.89–2.04, <i>p</i> = 0.15)	6.5	3.7	0.05
Pulmonary fibrosis/interstitial disease	7.59 (0.99–58.05, 0.05)	1.93 (0.61–6.13, <i>p</i> = 0.26)	0.3	0.6	1.00
Liver disease	5.33 (2.36–12.06, <i>p</i> = 0.0001)	1.25 (0.79–1.96, <i>p</i> = 0.34)	3.3	2.6	0.54
Gastrointestinal bleeding	3.91 (0.93–16.58, <i>p</i> = 0.06)	2.00 (1.12–3.56, <i>p</i> = 0.02)	0.7	1.7	0.26
Renal disease	2.74 (1.47–5.13, <i>p</i> = 0.001)	1.42 (1.05–1.93, <i>p</i> = 0.02)	4.9	6.2	0.48
Connective tissue/musculoskeletal	1.68 (1.13–2.49, <i>p</i> = 0.01)	1.29 (1.07–1.54, <i>p</i> = 0.006)	23.5	21.7	0.52
Osteoporosis	2.11 (0.82–5.41, <i>p</i> = 0.12)	1.60 (0.97–2.63, <i>p</i> = 0.07)	2.6	2.0	0.50
Peripheral vascular disease	0.86 (0.48–1.54, <i>p</i> = 0.60)	0.89 (0.69–1.14, <i>p</i> = 0.36)	10.8	10.0	0.74

¹Each estimate is adjusted for age, gender, smoking status and histology. ²Fisher's exact test *p* value.

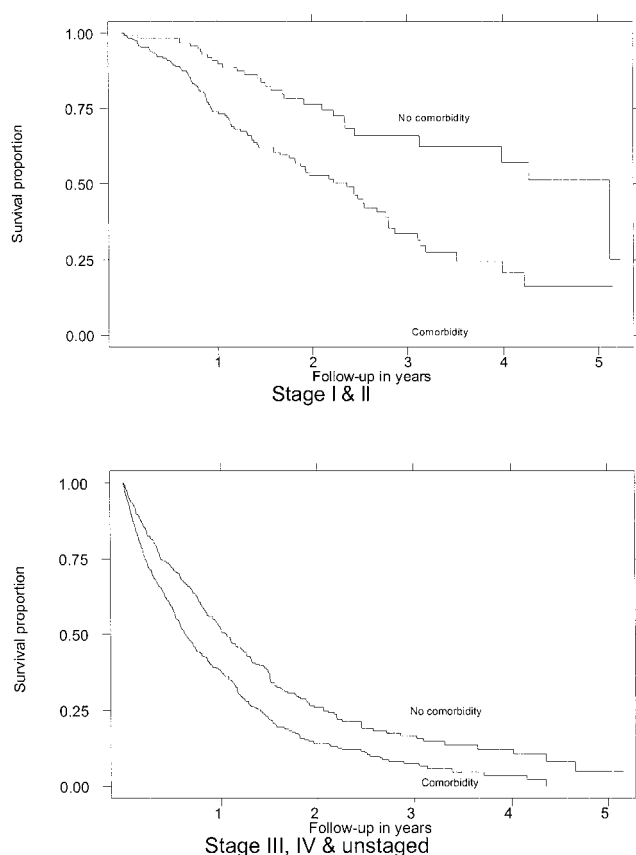


FIGURE 3 – Survival plots for patients with ≥ 1 vs. 0 adverse comorbidities (*i.e.*, the 18 listed in Table II excluding peripheral vascular disease) stratified by early- and late-stage disease and adjusted for age, gender, smoking status and histology (for both, *p* < 0.001).

of specific mechanisms leading from comorbidity to decreased survival, and effective interventions are based on an understanding of these mechanisms.

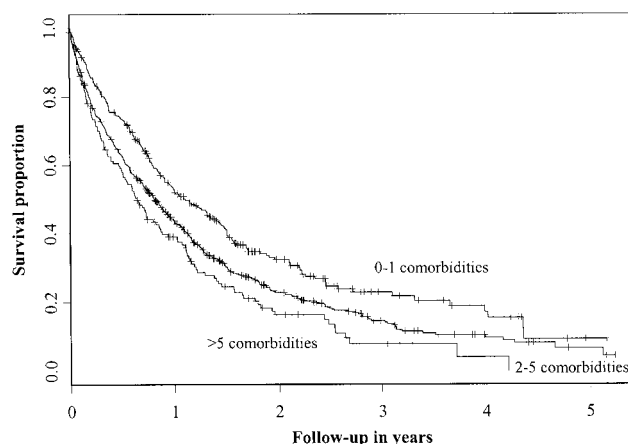


FIGURE 4 – Kaplan-Meier survival plot for 1,155 lung cancer patients stratified by comorbidity count (log rank test *p* < 0.0001).

To reduce the chance of overfitting survival models, Harrell *et al.*⁷⁵ recommended a minimum of 10 events for each predictor variable in the complete model before any selection takes place. In their study, 56 comorbidities were evaluated and 807 events had occurred in the data analyzed in the largest model. Even though their guidelines were met, there still exists a possibility that some of the effects found to be important in our study were due to chance and multiple comparisons. To help identify associations in which we should and should not place confidence, bootstrap HR estimates and CIs were prepared. They provide some direction but cannot substitute for confirmatory studies in different settings.

The prognostic effects of the 19 predictive comorbidities, especially pulmonary fibrosis and asthma, need verification. Ten comorbidities had elevated HRs (range 1.20–1.91), but their CIs were too large to draw conclusions (Table II). The importance of these 10 comorbidities needs to be clarified in more powerful studies. Also, the effects of the 27 comorbidities not strongly associated with survival (Table II) need confirmation. Some important comorbidities, such as connective tissue/musculoskeletal diseases, need further subclassification to more precisely characterize which distinct diseases drive the damaging effects. COPD

was reported in 28.6% of patients. However, in 66.4% of patients with COPD, no other specific respiratory diagnosis was reported. It appears that emphysema and chronic bronchitis are poorly classified, and this explains why COPD was a strong predictor of survival but emphysema and chronic bronchitis were not. The relationships of COPD, emphysema, chronic bronchitis and asthma with survival need detailed investigation.

The current analysis fails to capture graded differences within treatment groups; *e.g.*, a patient with COPD may receive a segmentectomy when a more extensive excision is indicated. Evaluation of alterations from optimal treatment may reveal further mechanisms by which comorbidity impacts survival. For the deleterious comorbidities whose effects were mediated through non-receipt of treatment or other comorbidities, the current study did not describe which specific treatments or which particular other comorbidities were involved. This work needs to be undertaken.

In conclusion, comorbidity is common in lung cancer patients and has a major impact on their survival. In multivariate analysis, 18 comorbidities were associated with an important reduction in lung cancer survival and 1 or more of these deleterious comorbidities was present in 64% of patients. Considering the relative amounts of survival variation explained by prognostic factors, comorbidity was only surpassed by stage and receipt of cancer treatment and explained as much variation as age, gender, smoking status and histology combined. Several uncommon comorbidities,

which have received little attention in previous studies, in aggregate affected a considerable proportion of lung cancer patients and explained an important amount of the survival variation. These findings, if confirmed, have clinical and research implications. It is hoped that further detailing of the effect of comorbidity in lung cancer patients will help guide therapeutic approaches that will improve care, which might include more intensive monitoring, aggressive treatment of important comorbidities and a resolute effort to provide patients with optimal cancer treatment. Because comorbidity appears to be such an important predictor of lung cancer survival, it should be taken into account in the design and analysis of clinical trials and other survival studies. Comorbidity has the potential to confound results if randomization is unbalanced, to be an effect modifier of treatments and even to influence study participation and thus impact the generalizability of findings. Research to establish and develop the current findings is needed and is expected to lead to interventions that will improve the grave prognosis associated with lung cancer.

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