Prognostic Importance of Comorbidity in a Hospital-Based Cancer Registry

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For more than 40 years, cancer patients have been staged by the size of their tumor while how sick they are from the tumor and other medical conditions were ignored. The present system of cancer classification does not consider the important patient-based prognostic factors, such as the general health of the patient, defined as the number and pathological severity of coexisting diseases, illnesses, or conditions. These conditions and diseases, which exist before cancer diagnosis and are not adverse effects of cancer treatment, are generally referred to as comorbidities.

While a routine consideration in selecting treatment and clinical decision-making, comorbidity is generally not considered in the design of cancer data sets or included in observational research. In many cases, comorbid health problems may be so severe as to impact directly on survival or prohibit the use of preferred antineoplastic therapies. Precise comorbidity information, along with patient demographics, behavioral risk characteristics, site of cancer, and morphologic stage of the tumor, is essential for comprehensive risk adjustment in cancer. Accurate risk adjustment is necessary for observational and health services research, including comparison of outcomes of different treatments and quality assessment.

Comorbidity is particularly important in elderly patients who have cancers that are biologically indolent or morphologically localized (ie, not rapidly fatal). Examples of such cancers include prostate, colon, oral cavity, pharynx and larynx, urinary bladder, ovary, uterus, breast, and non-Hodgkin lymphoma. Based on recent cancer incidence rates, these cancers represent approximately 61% of all cancers for men and 65% for women. Therefore, it is essential that comorbidities be accounted for when evaluating outcomes and quality of care for patients with cancer.

National and international cancer organizations are interested in adding comorbidity as a required data element in cancer registries. For example, the Commission on Cancer (COC) mandated that comorbidity and complication information must be included in all COC-approved hospital-based cancer registries.
IMPORTANCE OF COMORBIDITY IN A HOSPITAL-BASED CANCER REGISTRY

based cancer registry programs starting with cases diagnosed on or after January 1, 2003. In June 2003, the National Health Service of the United Kingdom decided to add a chart-based comorbidity collection system for use in their new cancer data set.

Our goal for this study was to assess whether comorbidity information obtained by cancer registrars during their usual chart abstraction process can provide important prognostic information. Improved descriptions of the patient with cancer, in addition to descriptions of the tumor, will result in improved prognostic stratification, which will allow for more accurate estimates of treatment effectiveness, prognosis, and assessment of quality of care.

METHODS
Study Design and Description of Database

Our study was a prospective cohort study of adults presenting to the Barnes-Jewish Hospital, Washington University School of Medicine, or the Siteman Cancer Center, St Louis, Mo, for primary diagnosis and treatment of new cancers of the prostate, respiratory tract, breast (female), digestive system, gynecological, urinary system, and head and neck between January 1, 1995, and January 31, 2001. A total of 19,268 patients received care and were eligible for the study. Of these patient records, 15,566 (8.0%) were excluded due to missing or unknown data for 1 or more of the following variables: race (0.6%), tumor stage (4%), or comorbidity information (7%), leaving a total of 17,712 patient records.

The Barnes-Jewish Hospital Oncology Data Services is an American College of Surgeons COC-approved tumor registry. The Oncology Data Services certified tumor registrars are responsible for collecting the required data elements for all patients with cancer from review of the medical record. The data items, coding rules, codes, and definitions used in the abstraction of all information, except comorbidity, were based on the detailed specifications provided by the Registry Operations and Data Standards committee of the standards of the COC.

Comorbidity Classification

In 1995, the certified tumor registrars at Barnes-Jewish Hospital in St Louis, Mo, were trained to code comorbidity from the review of the medical record during the usual chart abstraction process. The following year, we received a National Cancer Institute education training award to produce a comorbidity coding training program based on our experience. This program was designed for use by cancer registrars and other health care professionals. The program consists of a training video, comorbidity data collection form, and workbook, which may be viewed at http://cancercomorbidity.wustl.edu/web_courses_support/ComorbidityCoding/. Registrars received instruction on how to collect information on 27 different comorbid ailments from the medical record.

Definition of Variables

Age at diagnosis, sex, and race were the primary demographic variables used in this study. Tumor, treatment, and follow-up data included date of initial diagnosis, primary tumor site, anatomical extent of the tumor or stage, course of treatment, and date of last contact or death. Primary tumor site and anatomical subsite were defined by the International Classification of Disease for Oncology, Second Revision (ICD-O-2) topography and morphology codes. Anatomical extent of the tumor was defined by the summary stage (local, regional, or distant) variable. The primary end point was duration of overall survival. Duration of survival was calculated in months and survival data were censored at the...
time of last follow-up. The National Death Index is used by the Oncology Data Services to obtain vital status information; cause of death is not routinely obtained.

Data Extraction and Analytical Plan
Standard descriptive statistics were used to describe the study population. To demonstrate the prognostic implication of comorbidity on survival, adjusted Kaplan-Meier survival curves were generated for each level of comorbidity, controlling for age, race, sex, and cancer stage, for the entire population. The likelihood ratio \( \chi^2 \) statistic was used to test the statistical significance of the observed survival differences across comorbidity levels. Two-tailed tests of significance were used, and significance was established at the \( P \leq 0.05 \) level.

Cox proportional hazards regression modeling was used to test the independent contribution of comorbidity on survival. The assumptions of the Cox proportional hazards regression model were examined statistically. The test for comorbidity was accomplished using a partial likelihood ratio \( \chi^2 \). Dummy variables were created for variables that had more than 2 reference categories or levels. For each variable, the category with the lowest mortality risk was assigned the reference value of 1.0. Adjusted hazard ratios (HRs) were then calculated with 95% confidence intervals (CIs) to represent independent trends in risk by age, race, sex, comorbidity level, tumor site, and tumor stage.

The prognostic discriminatory capacity of all models was represented by the \( c \) statistic or concordance index. Discrimination refers to the ability of the model to separate those patients who live from those who die. The \( c \) statistic is identical to the area under a receiver operating characteristic curve, a widely used measure of diagnostic discrimination. The \( c \) statistic ranges from 0.5 to 1.0; a value of 0.5 indicates random predictions and a value of 1.0 indicates perfect separation of patients who die from patients who survive. A model with a \( c \) statistic value of more than roughly 0.8 has some use in predicting the response of individual patients. Computation of the \( c \) statistic for survival analysis is available as a Stata version 7.0 automatic do file. All other statistical analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC). Washington University Human Studies Committee approval was obtained to train registrars in comorbidity collection and to abstract patient information.

RESULTS

Description of the Population
The population of 17712 patients with cancer in the Barnes-Jewish Hospital tumor registry is described in Table 1. The mean and median duration of follow-up for patients alive at the time of analysis was 35 and 31 months, respectively. As expected, the population consisted of a significant number of elderly patients (46.3% aged 65 years or older) and the racial distribution reflects the metro St Louis, Mo, and Midwest region. The frequency distribution of the severity of comorbidity was none (45.5%), mild (29.8%), moderate (17.3%), and severe (7.4%). In Table 2, the distribution of tumor sites is shown. The most frequent tumor was prostate (23.8%), followed by lung (17.9%), breast (16.0%), digestive system (14.4%), and gynecological (14.3%) tumors. Hypertension was the most frequently reported comorbid ailment (38%), followed by previous solid tumor (13%) and diabetes mellitus (11%).

Prognostic Impact
The relationship between patient and tumor factors and overall survival is shown in Table 1. As represented by the unadjusted HRs (where the higher the ratio, the more number of deaths) from the Cox proportional hazards regression analysis, overall survival is inversely related to increasing age, race, severity of comorbidity, and morphologic extent of tumor. Compared with patients classified in overall comorbidity severity none, the unadjusted HR associated with mild comorbidity was 1.42 (95% CI,

| Table 1. Description of the Population and Relationship of Baseline Demographic, Clinical, Tumor, and Treatment Characteristics to Overall Survival (N = 17712) |
|-------------|-----------------|-----------------|
| Age, y      | No. (% of Patients) | Unadjusted Hazard Ratio (95% CI) |
| <50         | 2988 (16.9)       | 1.00            |
| 50-64       | 6511 (36.8)       | 1.17 (1.07-1.28) |
| 65-74       | 5159 (29.1)       | 1.53 (1.40-1.67) |
| ≥75         | 3054 (17.2)       | 2.74 (2.50-3.00) |
| Race        |                  |                 |
| White       | 14334 (80.9)      | 1.00            |
| Black       | 3378 (19.1)       | 1.59 (1.49-1.69) |
| Sex         |                  |                 |
| Male        | 8988 (50.8)       | 1.00            |
| Female      | 8724 (49.3)       | 1.02 (0.97-1.08) |
| Comorbidity level |                  |                 |
| None        | 8051 (45.5)       | 1.00            |
| Mild        | 5286 (30.9)       | 1.42 (1.38-1.54) |
| Moderate    | 3058 (17.3)       | 2.12 (1.97-2.27) |
| Severe      | 1317 (7.4)        | 3.27 (2.99-3.56) |
| Tumor stage |                  |                 |
| In situ     | 805 (4.5)         | 1.00            |
| Localized   | 8565 (48.4)       |                 |
| Regional by direct extension | 2478 (14.0) | 2.22 (2.03-2.44) |
| Regional to lymph nodes    | 1722 (9.7)       | 3.16 (2.87-3.47) |
| Regional by direct extension and to lymph nodes | 1508 (8.5) | 5.59 (5.12-6.11) |
| Distant metastases/systemic disease | 2634 (14.9) | 12.76 (11.9-13.7) |

Abbreviation: CI, confidence interval.
1.38–1.54); moderate, 2.12 (95% CI, 1.97–2.27); and severe, 3.27 (95% CI, 2.99–3.56).

The Kaplan-Meier survival curve for all patients and the adjusted Kaplan-Meier curves for each level of comorbidity are shown in the FIGURE. At any point in time, the patients with more severe levels of comorbidity had worse survival (partial $\chi^2$ due to comorbidity, 523.54; $P<.001$). The 3-year adjusted overall survival rate for patients in category none was 78%, although the rate for severe category was 54%, a difference of 24%. The difference in the 5-year adjusted overall survival rates between patients with comorbidity severity level none and those with level severe was 33%.

In TABLE 2, the distribution of patients according to site of primary tumor is shown. For each site, adjusted HRs and their associated CIs are displayed. The frequency of patients with moderate or severe comorbidity varied across tumor sites from 42.9% for patients with urinary system tumors to 39.6% for lung tumors, 18.8% for breast tumors, and 13.2% for prostate tumors. The partial $\chi^2$ due to comorbidity ranged from 17.32 for gynecological tumors to 155.66 for prostate tumors (all $P<.001$).

In general, increasing adjusted HRs for increasing levels of comorbidity severity is demonstrated. The differential prognostic impact of comorbidity can be observed by examining the HRs for severe comorbidity (relative to none). These HRs varied from a low of 1.48 for lung cancer to a high of 9.21 for prostate cancer. Measured by the $c$ statistic, model discrimination varied from 0.71 for head and neck to 0.86 for prostate tumors. Across all cancer sites, the addition of comorbidity information improved the discrimination of the prognostic models.

We also examined the impact of severity of comorbidity on development of recurrence, an important cancer-related outcome. Of the 17712 patients, 5058 (28.5%) developed a cancer recurrence. The number and rates of recurrence among the different levels of comorbidity severity were 2026 (25%) for none, 1534 (29%) for mild, 976 (32%) for moderate, and 522 (40%) for severe categories. After adjusting for extent of disease and
treatment, the adjusted odds ratios for developing recurrence according to increasing levels of comorbidity with none category as the referent were 1.18 (95% CI, 1.07–1.30) for mild, 1.37 (95% CI, 1.22–1.53) for moderate, and 1.54 (95% CI, 1.31–1.80) for severe. The c statistic for the recurrence model with extent of disease, treatment, and comorbidity was 0.85.

**COMMENT**

Our results demonstrate that hospital-based cancer registrars can collect comorbidity information, which provides important prognostic information. Comorbidity information was prognostically relevant in all cancer sites while the exact contribution varied from site to site. Comorbidity information was more important among the cancers with longer mean survival (prostate and breast) and prognostically least informative in the cancers with the worst survival (lung). In addition, we showed that comorbidity and extent of tumor spread or stage are prognostically complementary.

Comorbidity information can be added to staging systems or incorporated into decision making programs to aid in patient consultation and improve patient decision making. Improved descriptions of the patient with cancer results in improved prognostic stratification, which will allow for more accurate estimates of treatment effectiveness when conducting outcomes research and analyzing results from observational hospital-based tumor registries.

The comorbidity information for this study was obtained through a detailed review of the medical record and other information available to cancer registrars as they performed their usual abstraction process. All participating registrars had successfully completed a comorbidity education program before the initiation of comorbidity coding. An emphasis of this program is the differentiation of preexisting medical conditions from symptoms and conditions related to the cancer or cancer care. The most frequently referenced chart-based comorbidity instruments are Kaplan-Feinstein Comorbidity Index,26 Charlson Comorbidity Index,27 and the Index of Co-Existent Disease.36 The Kaplan-Feinstein Comorbidity Index was developed from a study of the impact of comorbidity on outcomes for patients with diabetes mellitus. Specific diseases and conditions are classified as mild, moderate, or severe, according to the pathophysiological severity of organ decompensation.

The Kaplan-Feinstein Comorbidity Index was created from the study of 1-year all-cause mortality in a cohort of 559 patients admitted to a medical unit of a teaching hospital with a variety of different medical conditions. It is a weighted index that takes into account the number and seriousness of various comorbid diseases and conditions. The Index of Co-Existent Disease attempts to predict length of stay and resource utilization after hospitalization.

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>No. (%)</th>
<th>Comorbidity Level</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 17 712)</td>
<td>8051 (45.5)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>5286 (29.8)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>3058 (17.3)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1317 (7.4)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Lung (n = 2771)†‡§</td>
<td>865 (31.2)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>811 (29.3)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>703 (25.4)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>392 (14.2)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Breast (n = 2839)†</td>
<td>1521 (53.6)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>784 (27.6)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>378 (13.3)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>156 (5.5)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Digestive system (n = 2550)</td>
<td>970 (38.0)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>840 (32.9)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>510 (20.0)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>230 (9.02)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Gynecological (n = 2535)</td>
<td>1324 (52.2)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>691 (27.3)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>409 (16.1)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>111 (4.4)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Urinary system (n = 1334)</td>
<td>408 (30.6)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>381 (28.6)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>357 (28.8)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>188 (14.1)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
<tr>
<td>Head and neck (n = 1086)</td>
<td>500 (46.0)</td>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>324 (29.8)</td>
<td>Mild</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>188 (17.3)</td>
<td>Moderate</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>74 (6.8)</td>
<td>Severe</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
+Hazard ratios are adjusted for age (continuous variable), race, sex, and cancer stage.
†Excludes 391 patients with lung tumors not of non–small cell type.
‡Includes 8051 patients with lung tumors not of non–small cell type.
§All are P<.001.

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Ninth Revision, Clinical Modification
International Classification of Diseases, bidity data is the first 6 secondary proach in which the source of comor-
tributor to transcribe and is easy for the cancer reg-
many years of hospitalization can be in-
for all patients who are hospitalized, ICD-9
advantage of this approach is that the
hospitalization discharge record. The
iest programs in the United States. The
approved hospital-based cancer regis-
ter registries. The
icmorbidities. " Specifi-
are never complete or detailed enough
strategy for identifying comorbidities. " Specifi-
cally, the ICD-9 system is used for hos-
pital billing and is designed to maxi-
mize financial revenue for the hospital, rather than accurately reflecting the pa-
tient's medical condition. In addi-
tion, the ICD-9 system labels diseases and conditions but does not capture
pathophysiological severity, and the listed conditions may actually be com-
plications of the index disease and hos-
pitalization rather than preexisting co-
morbid conditions. Therefore, the
hospital discharge record may be an in-
accurate, incomplete, and misleading
record of comorbid conditions at the
time of diagnosis.

Previous research has demon-
strated that the severity of comor-
bitality can significantly alter the type of
initial antineoplastic treatment. For ex-
ample, Desch et al studied treatment
recommendations for local and re-
regional prostate cancer and found that
treatment recommendations were of-
ten based on the overall health of the
patient and not based solely on the ex-
tent of the spread of the tumor. As co-
morbidity increased, the proportion of
men receiving no treatment increased
correspondingly. Less than 30% of men
with the most significant level of co-
morbidity received surgery, radiation
therapy, or combinations of aggres-
sive therapy compared with almost 55% of
men who had no comorbid ailments. Van Spronsen et al studied a popula-
tion-based series of patients with
Hodgkin disease and non-
Hodgkin lymphoma diagnosed be-
tween 1993 and 1996. In the presence of comorbidity, 50% less chemo-
otherapy was administered to elderly pa-
tients with Hodgkin disease and 10%
to 15% less to elderly patients with non-
Hodgkin lymphoma.

The prognostic impact of comorbid-
ity is believed to be due to the physi-
ological burden of chronic disease and its interaction with the cancer and its
treatment. Increasing severity of co-
morbidity may increase the toxicity of
specific treatments and may suffi-
ciently shorten remaining life expec-
tancy to cancel gains with therapy. It
is also possible that the negative pro-
gnostic impact of severe comorbidity is
actually due to the use of less ideal or
aggressive therapy. That is, patients
with multiple medical comorbidities
and severe decompensation do not re-
ceive appropriate therapy, thus mak-
ing it difficult to discern whether the
decrease in survival is due to the co-
morbidity or less aggressive treat-
ment. In previous research, we dem-
strated that the prognostic impact of
comorbidity in head and neck cancer
was not due to less aggressive therapy.

The limitations of our research are
that it reports from a single academic
medical center site and does not com-
pare the prognostic estimates ob-
tained through chart-based approach
using the ACE-27 to a claims-based
approach using the ICD-9 codes. Al-
though this report is from a single site,
it does replicate the findings from a pre-
vious study of comorbidity assess-
ment at several community hospitals.
A comparison of the ability of 2 differ-
ent systems of comorbidity assess-
ment (chart-based and claims-based) is
an extremely interesting question. Sev-
eral different national cancer organi-
izations, such as the American College
of Surgeons COC, National Cancer In-
stitute Surveillance, Epidemiology, and
End Results, and the Centers for Dis-
ease Control and Prevention National
Program of Cancer Registries, man-
dated or are considering the require-
ment for comorbidity data collection.
The findings from high-quality re-
search into the impact of different meth-
ods of collection would help these or-
ganizations select the best method for
comorbidity collection.

In conclusion, our experience dur-
ing the past 7 years demonstrates that
comorbidity information can be col-
lected by cancer registrars as part of
their usual chart abstraction process and
that comorbidity information can be
combined with other demographic and
tumor information to provide a more
complete description of the patient with
cancer. Comorbidity information can
improve prognostic estimates derived
from cancer registries and allow for
more accurate risk adjustment and as-
essment of quality of care.
Author Contributions: Dr Piccirillo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Piccirillo, Costas.

Acquisition of data: Piccirillo, Grove.

Analysis and interpretation of data: Piccirillo, Tierney, Costas, Spitznagel.

Drafting of the manuscript: Piccirillo, Tierney, Costas, Grove.

Critical revision of the manuscript for important intellectual content: Piccirillo, Spitznagel.

Statistical expertise: Piccirillo, Costas, Spitznagel.

Obtained funding: Piccirillo.

Administrative, technical, or material support: Tierney, Grove.

Supervision: Piccirillo.

Funding/Support: This work was supported by a cancer education-training award (R25CA68304-01) from the National Cancer Institute.

Role of the Sponsor: The National Cancer Institute did not participate in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Additional Information: Interested readers may view the ACE-27 at http://oto.wustl.edu/clinipe /Forms/com_form.doc. Adjusted Kaplan-Meier survival curves for each anatomic site are available from the authors.

REFERENCES


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(Reprinted) JAMA, May 26, 2004—Vol 291, No. 20 2447