Prognostic Importance of Comorbidity in a Hospital-Based Cancer Registry

Jay F. Piccirillo, MD
Ryan M. Tierney, MD
Irene Costas, MPH
Lori Grove, CTR
Edward L. Spitznagel, Jr, PhD

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, 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.

Context Patients with cancer often have other medical ailments, referred to as comorbidity. Comorbidity may impact treatment decision-making, prognosis, and quality of care assessment.

Objective To assess whether comorbidity information can provide important prognostic information in a hospital-based cancer registry.

Design, Setting, and Participants An observational prospective cohort study using comorbidity data collected by trained hospital-based cancer registrars. Comorbidity was obtained through medical record review using the Adult Comorbidity Evaluation 27, a validated chart-based comorbidity instrument. A total of 17712 patients receiving care between January 1, 1995, and January 31, 2001, for the primary diagnosis of new cancer of the prostate, lung (nonsmall cell), breast, digestive system, gynecological, urinary system, or head and neck were included.

Main Outcome Measure Duration in months of overall survival.

Results A total of 19268 patients were included in the study; median duration of follow-up was 31 months. Of these patients, 1556 (8.0%) were excluded due to missing or unknown data. Severity of comorbidity strongly influenced survival in a dose-dependent fashion and the impact of comorbidity was independent of cancer stage. Compared with patients without comorbidity, the adjusted hazard ratio associated with mild comorbidity was 1.21 (95% confidence interval [CI], 1.13-1.30), moderate comorbidity was 1.86 (95% CI, 1.73-2.00), and severe comorbidity was 2.56 (95% CI, 2.35-2.81). Adjusted Kaplan-Meier survival curves revealed that at any point in time the patients with more severe levels of comorbidity had worse survival (partial F3 due to comorbidity, 523.54; P<.001). Model discrimination ranged from 0.71 for head and neck to 0.86 for prostate cancers.

Conclusions Comorbidity is an important independent prognostic factor for patients with cancer. The inclusion of comorbidity in hospital-based cancer registries will increase the value and use of observational research.

JAMA. 2004;291:2441-2447 www.jama.com

©2004 American Medical Association. All rights reserved.
IMPORTANCE OF COMORBIDITY IN A HOSPITAL-BASED CANCER REGISTRY

Klabunde CN, Wingo PA, Horn RC, et al.

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 19268 patients received care and were eligible for the study. Of these patient records, 1556 (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 17712 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.23

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.24 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. In addition, emphasis was placed on how to differentiate comorbidities from medical conditions related to the index cancer and symptoms related to cancer development or adverse effects of cancer treatment. A chart-based approach to comorbidity collection was selected for 2 reasons. First, registrars are already reviewing the medical record for tumor and treatment information and so the identification and abstraction of comorbidity information would not be unduly burdensome. Second, previous research25 demonstrated that the claims-based approach underestimated the number of comorbid ailments identified using a medical record abstraction process in men undergoing prostatectomy.

The cogent comorbid ailments were selected based on previous research by Kaplan and Feinstein,26 Charlson et al,27 Elixhauser et al,28 Fleming et al,6 and Klabunde et al,29 and the clinical judgment of 1 of the authors (J.F.P.) and other clinical cancer experts at Washington University. Ailments were selected based on the frequency of occurrence and the clinical implications for the newly diagnosed patient with cancer.

To identify the individual comorbid ailments and define the severity of comorbid health, the registrars were trained and validated in the use of the Adult Comorbidity Evaluation 27 (ACE-27). The ACE-27 is a new 27-item validated comorbidity index for use with patients with cancer. We have previously demonstrated the ability of cancer registrars at nonacademic medical centers to collect comorbid health information accurately and efficiently from the medical record with the ACE-27.30 The ACE-27 grades specific diseases and conditions into 1 of 3 levels of comorbidity, grade 1 (mild), grade 2 (moderate), or grade 3 (severe), according to the severity of individual organ decompensation and prognostic impact. Once the patient’s individual diseases or comorbid conditions are classified, an overall comorbidity score (none, mild, moderate, or severe) is assigned based on the highest ranked single ailment. In the cases in which 2 or more moderate ailments occur in different organ systems or disease groupings, the overall comorbidity score is designated as severe. Comorbidity assessment was performed through a review of the medical records and other health information sources that registrars use to obtain the COC-required data elements.

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.31 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\(^3\) 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 method\(^2\) 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 assess the statistical significance of the observed survival differences across comorbidity levels. Two-tailed tests of significance were performed, 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.\(^3\) 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.\(^3\) Computation of the \(c\) statistic for survival analysis is available as a Stata version 7.0 automatic do file.\(^2\) 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 17 712 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,
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 3, the distribution of comorbidity and association with overall survival for the entire cohort and within each major tumor site 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, Charlson Comorbidity Index, and the Index of Co-Existing Disease. 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 Charlson 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-Existing Disease attempts to predict length of stay and resource utilization after hospitalization.

**Table 3. Overall Survival as a Function of Severity of Comorbidity for All Patients and Each Tumor Site**

<table>
<thead>
<tr>
<th>Comorbidity Level</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 17 712)</td>
<td>8051 (45.5)</td>
<td>5286 (29.8)</td>
<td>3058 (17.3)</td>
<td>1317 (7.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.21 (1.13–1.30)</td>
<td>1.86 (1.73–2.00)</td>
<td>2.56 (2.35–2.81)</td>
</tr>
<tr>
<td>Prostate (n = 4206)</td>
<td>2325 (55.3)</td>
<td>1328 (31.6)</td>
<td>431 (10.3)</td>
<td>122 (2.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.55 (1.16–2.07)</td>
<td>3.96 (2.84–5.24)</td>
<td>9.21 (6.48–13.11)</td>
</tr>
<tr>
<td>Lung (non–small cell) (n = 2771)</td>
<td>865 (31.2)</td>
<td>811 (29.3)</td>
<td>703 (25.4)</td>
<td>392 (14.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.08 (0.96–1.22)</td>
<td>1.19 (1.05–1.35)</td>
<td>1.48 (1.27–1.71)</td>
</tr>
<tr>
<td>Breast (n = 2839)</td>
<td>1521 (53.6)</td>
<td>784 (27.6)</td>
<td>378 (13.3)</td>
<td>156 (5.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.97 (0.88–1.14)</td>
<td>1.83 (1.37–2.45)</td>
<td>1.98 (1.36–2.88)</td>
</tr>
<tr>
<td>Digestive system (n = 2550)</td>
<td>970 (38.0)</td>
<td>840 (32.9)</td>
<td>510 (20.0)</td>
<td>230 (9.02)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.13 (0.97–1.31)</td>
<td>1.41 (1.20–1.66)</td>
<td>1.73 (1.40–2.13)</td>
</tr>
<tr>
<td>Gynecological (n = 2535)</td>
<td>1324 (52.2)</td>
<td>691 (27.3)</td>
<td>409 (16.1)</td>
<td>111 (4.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.13 (0.94–1.35)</td>
<td>1.24 (1.00–1.54)</td>
<td>2.04 (1.47–2.82)</td>
</tr>
<tr>
<td>Urinary system (n = 1334)</td>
<td>408 (30.6)</td>
<td>381 (28.6)</td>
<td>357 (28.8)</td>
<td>188 (14.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.02 (0.79–1.33)</td>
<td>1.37 (1.06–1.78)</td>
<td>1.97 (1.49–2.62)</td>
</tr>
<tr>
<td>Head and neck (n = 1086)</td>
<td>500 (46.0)</td>
<td>324 (29.8)</td>
<td>188 (17.3)</td>
<td>74 (6.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.03 (0.80–1.32)</td>
<td>1.92 (1.50–2.47)</td>
<td>2.48 (1.77–3.47)</td>
</tr>
</tbody>
</table>

©2004 American Medical Association. All rights reserved.

(Reprinted) JAMA, May 26, 2004—Vol 291, No. 20 2445
IMPORTANCE OF COMORBIDITY IN A HOSPITAL-BASED CANCER REGISTRY

ization. To calculate the overall level of comorbidity, Index of Co-Existing Disease assesses the patient’s status in 2 separate components: physiological and functional burden. Scores from the 2 components are combined to produce a composite score. The ACE-27 is the comorbidity instrument used by the cancer registrars at Barnes-Jewish Hospital and was developed through modifications and additions of comorbid ailments to the Kaplan-Feinstein Comorbidity Index. The ACE-27 includes many important comorbid conditions, such as dementia, diabetes mellitus, and AIDS that are not included in the Kaplan-Feinstein Comorbidity Index. The grading of the pathophysiological severity of the newly added ailments was performed through expert opinion and review of the medical literature. The prognostic use of the ACE-27 has been previously validated.

Comorbidity information is a new data element recently mandated for inclusion in the more than 1400 COC-approved hospital-based cancer registry programs in the United States. The COC has chosen the claims-based approach in which the source of comorbid ailments is the first 6 secondary COC has chosen the claims-based approach. In fact, 2 studies demonstrated that the severity of comorbidity can significantly alter the type of initial antineoplastic treatment. For example, Desch et al studied treatment recommendations for local and regional prostate cancer and found that treatment recommendations were often based on the overall health of the patient and not based solely on the extent of the spread of the tumor. As comorbidity increased, the proportion of men receiving no treatment increased correspondingly. Less than 30% of men with the most significant level of comorbidity received surgery, radiation therapy, or combinations of aggressive therapy compared with almost 55% of men who had no comorbid ailments. Van Spronsen et al studied a population-based series of patients with Hodgkin disease and non-Hodgkin lymphoma diagnosed between 1993 and 1996. In the presence of comorbidity, 50% less chemotherapy was administered to elderly patients with Hodgkin disease and 10% to 15% less to elderly patients with non-Hodgkin lymphoma.

The prognostic impact of comorbidity is believed to be due to the physiological burden of chronic disease and its interaction with the cancer and its treatment. Increasing severity of comorbidity may increase the toxicity of specific treatments and may sufficiently shorten remaining life expectancy to cancel gains with therapy. It is also possible that the negative prognostic 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 receive appropriate therapy, thus making it difficult to discern whether the decrease in survival is due to the comorbidity or less aggressive treatment. In previous research, we demonstrated 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 compare the prognostic estimates obtained through chart-based approach using the ACE-27 to a claims-based approach using the ICD-9 codes. Although this report is from a single site, it does replicate the findings from a previous study of comorbidity assessment at several community hospitals. A comparison of the ability of 2 different systems of comorbidity assessment (chart-based and claims-based) is an extremely interesting question. Several different national cancer organizations, such as the American College of Surgeons COC, National Cancer Institute Surveillance, Epidemiology, and End Results, and the Centers for Disease Control and Prevention National Program of Cancer Registries, mandated or are considering the requirement for comorbidity data collection. The findings from high-quality research into the impact of different methods of collection would help these organizations select the best method for comorbidity collection.

In conclusion, our experience during the past 7 years demonstrates that comorbidity information can be collected 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 assessment of quality of care.
References


42. Iezzoni LI. The risks of risk adjustment. JAMA. 1997;278:1600-1607.


