Comorbidity Considerations in Geriatric Oncology Research

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ABSTRACT Although it is generally acknowledged that comorbidity has a significant impact on treatment selection and outcomes for elderly patients with cancer, an understanding of how comorbid conditions should influence clinical decisions is quite incomplete. This issue remains an important and challenging area of geriatric oncology research. Measures of comorbidity require recognition, documentation, and accurate data extraction. Extensive prospective evaluations and medical chart reviews have the greatest reliability but are costly. Administrative data are convenient and applicable to large populations, but suffer from relatively poor reliability and therefore should be used with caution. Perhaps in the future more refined nosology and better information systems will improve our understanding and ability to use administrative data sets to study comorbidity in the elderly—the eventual goal of such investigation being evidence-based criteria for care of elderly cancer patients.

BACKGROUND

Comorbidity may be defined as “the existence or occurrence of any distinct additional entity during the clinical course of a patient who has the index disease under study.”1 Unlike complications, which are sequellae of the principal diagnosis or its treatment, comorbidities are causally unrelated to the primary diagnosis.2 The type, number, and severity of comorbid conditions will determine the extent of their influence on treatment outcomes.3,4 The presence of comorbid conditions may adversely influence treatment choice through the selection of “too much or too little.” Such complications of cancer management can and do result in premature death for some patients.

As we age, the interface between health and illness blurs, and the balance gradually shifts from health to disease. While health is usually inversely related to age, disease is directly related to aging both in number and severity. The variety and severity of comorbid conditions found in elderly patients with cancer increase with advancing age.3,4 The presence of coexistent disease when cancer is diagnosed influences treatment selection, affects patient response and survival rates, and plays a role in decision-making for the allocation of health care resources. In an attempt to avoid complications, clinicians may choose suboptimal anticancer therapies for their elderly patients who have other health problems (Figure 1). The complexity of the interaction of comorbid conditions and their medical management in the elderly patient with cancer are the focus of this review.

Although various malignant diseases vary greatly as to the age range of individuals likely to be affected, approximately 60 percent of newly diagnosed patients are at least 65 years of age.5 The older segment of the US population is growing
rapidly, and the incidence of cancer will no doubt increase dramatically as a result of this demographic change.\(^6\)

The classifications of cancer have developed into a useful tool for guiding both treatment and prognostic expectations. The classification of cancer traditionally includes the histology, organ of origin, and extent or stage of disease. Unfortunately, similar systems have not yet been devised for most comorbid conditions.

Health is easy to recognize, but illness may range from the obvious to the occult. Clear definitions of the type and severity of principal and comorbid diseases are necessary to understand their natural history and determine how specific interventions influence outcomes. The focus on episodic care by a health care system like ours that typically pays for one medical problem at a time detracts from our understanding of the longitudinal interactions among comorbid conditions.

For elderly people, this is a particular problem, because with age, they accumulate multiple medical problems. Measures of comorbidity are important considerations when evaluating the benefits and costs of both screening programs and cancer treatment studies, and when allocating the resources necessary to carry out both of these interventions. In the coming years, the medical resources required for diagnosis, initial treatment, and continuing care will only escalate. And the increase in life-threatening complications of therapy will lead to many more ethical dilemmas related to medical futility.

### TYPES OF COMORBID CONDITIONS

The list of comorbid conditions may be reduced to as few as 10, by lumping all of the abnormalities associated with a specific organ system: Neurological, gastrointestinal, pulmonary, cardiovascular, hepatic, genitourinary, musculoskeletal, cutaneous, hematologic, and endocrine. If specific symptoms, signs, and diseases are considered, the list could grow to over 100. The severity of the condition, whether it is a historical or active process, the requirement of treatment, and the effectiveness of the treatment for the comorbid condition are additional conditioners for the comorbid condition.

Some comorbid conditions may exacerbate the morbidity associated with the toxicity of anticancer treatments. For example, pneumonitis resulting from chemotherapy-induced leukopenia in a patient with chronic lung disease could prove life threatening. Renal, cardiac, or hepatic disease may limit the choice of specific chemotherapeutic agents in specific patients. Sometimes the comorbid conditions contributing to toxicity of treatment are metachronous or synchronous unrelated cancers. Cumulative toxicity of chemotherapy and radiotherapy may be a factor in patients with multiple primary malignancies, and may limit subsequent use of these modalities. Prior radiotherapy may increase complications of surgery in the irradiated field.

Both the number and type of comorbid conditions will influence the overall survival rate of patients even after statistical adjustments for age, sex, and stage of disease are made.\(^1\) In a population-based study of colorectal cancer patients that included chart reviews (in order to be inclusive of major comorbid conditions), the risk ratio for decreased survival became sta-

![FIGURE 1](image-url)

Confounding Bias Associated with the Intervention and the Outcome

**COMORBID CONDITIONS**

**POOR OUTCOMES**

**LESS TREATMENT SELECTED**

(?Suboptimal)

Stratification for comorbidity can control bias.

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istically significant when there were more than five comorbid conditions. Comorbid conditions that compromise patients the most include: Active cardiac disease, emphysema, renal disease, insulin-dependent diabetes mellitus, and interestingly, a history of a previous cancer. In colorectal cancer patients in this population, alcohol abuse, depression, and anemia were also predictors for poor survival rates. One could postulate that active alcoholics and depressed patients might be less compliant with optimal treatment interventions or suffer secondary dietary impairment from their comorbid conditions. The presence of anemia may be a surrogate for the continued loss of blood from the gastrointestinal tract or reflect the systemic depression of hematopoiesis.

For breast cancer the major comorbidities contributing to death at 30 months were similar to those found in colon cancer when major organ systems were compromised: Cardiovascular, pulmonary, renal, hepatic, and neurological. Asthma and smoking also appear to contribute to the decrease in survival rates in elderly patients. Interestingly, arthritis appears to afford some protection, perhaps reflecting on the increased use of aspirin for arthritic management.

Additional comorbid conditions common among the elderly and relevant to toxicity of or compliance with treatment include: Malnutrition, dementia, immobility, problems with gait and balance, incontinence, and sensory impairment.8,9

### AGE-RELATED FACTORS

For many cancers, a patient’s advanced chronological age is considered a major adverse prognostic factor. However, the relationship between age, tolerance of anticancer treatments, and clinical outcome is a complex one. Some studies have found that elderly patients face a greater risk of mortality from emergency surgical procedures. But after adjustment for patients with contraindications to surgery, mortality rates following elective surgery appear to be similar among elderly and younger patients, although the former require a longer period of recovery. Most elderly patients tolerate radiotherapy relatively well. Chemotherapy-induced myelosuppression in elderly patients with delayed recovery places them at increased risk of serious infectious and bleeding complications. However, adjustments in chemotherapy regimens can often be made to improve their tolerability among elderly patients. Likewise, the use of hematopoietic growth factors and other drugs that attenuate some toxicities of chemotherapy may be particularly valuable for some elderly patients.8

In other cases, cancers in the elderly seem to be biologically different from those in younger patients. Thus, the poor prognosis for elderly patients with acute leukemia is not merely due to inherent difficulties tolerating aggressive chemotherapy regimens; elderly patients are more likely to have cytogenetic findings associated with resistance to chemotherapy.10

Around the sixth and seventh decade of life, there is increasing variation between physiological and chronological age. Just as some people appear younger than their chronological age while others look older, age may also be discordant with physiological or functional

### TABLE 1

| Sources of Comorbidity Information | Patients | Providers | Administrators |
|-----------------------------------|----------|-----------|----------------|
| Medical History                   | Medical History | ICD-9 Codes* | Hospital Charts |
| Survey Results                    | Physical Examination | CPT Codes* | ICD-9 Codes* |
| Diagnostic Testing                | Clinical Judgment | DRG Codes* | CPT Codes* |
|                                  |                       | Utilization Data |                    |
|                                  |                       | Payor Reimbursement |                |
|                                  |                       | Hospital Stays |                |
|                                  |                       | Clinic Visits |                |
|                                  |                       | Diagnostic Tests |                |

*High potential for misclassification.
capacities. For this reason, consideration of physiological age and of comorbidities is especially important when selecting therapies for individual patients and when evaluating results of clinical trials.

SOURCES OF COMORBIDITY INFORMATION

Information on comorbidities can be obtained directly from patients, from providers’ records, and from administrative data. Two important sources of information about individual comorbidity are medical records and survey results (Table 1). Providers gather and integrate information from the history, physical examination, diagnostic testing, and by using their own clinical judgment. They use common disease definitions to group patients into categories relevant to clinical decisions. Providers and administrative staff also assign diagnosis and reimbursement codes. Administrators are then able to account for the resources necessary to successfully treat a particular disease or group of diseases.

Administrative data sets are commonly used to concisely summarize information from patient charts, primarily in hospitals and occasionally from providers’ offices. These data sets typically use surrogate codes that are generated primarily for reimbursement purposes (ICD-9, CPT, DRG). The coupling of administrative data codes with utilization information, such as hospital stays, clinical visits, diagnostic and therapeutic maneuvers, prescription drug records, and payor reimbursement transactions provide a useful database for analysis. This indirect information may be used as a benchmark for intra- and inter-institutional comparisons of resource utilization for similar diseases and treatments. Whether looking at trends in one or many institutions, administrators have found this technique useful as performance indicators and/or measures.

Contributions to descriptive data about comorbid conditions come from sources that vary in both reliability and validity. The reliability of the information from informed patients generally provides the greatest reproducibility and accuracy. But the elderly may have both information and cognitive deficits that can interfere with collection of accurate and complete data.

In this age of “managed costs,” the ability to assess patient groups sharing particular disease characteristics and similar treatments provides a quasi-reliable method to predict resource requirements. Because it is efficient and economical, this methodology is receiving increasing attention. Enhancing the accuracy of the descriptive data we have regarding treatment selection and effectiveness and the accompanying complications are the bare essentials for developing reliable predictive models for estimating future medical resource needs. Good strategic planning is needed to assure quality cancer care delivery for our aging population in the coming decades.

COMORBIDITY AND CLINICAL TRIALS

Prospective clinical trials that include patients with comorbid conditions of variable severity would be the ideal, but continued exclusion of those with moderate-to-severe comorbidity is likely to persist in an effort to clearly delineate the efficacy of the treatment under study. The presence of comorbid conditions sufficient to warrant clinical attention is likely to keep many elderly individuals from accessing screening studies and/or investigational therapy trials, as clinical investigators often place their primary focus on study completion, complications, cooperation, and cost factors.

The constellation of comorbidities encountered in the elderly influences selection of treatment as well as treatment outcomes; for this reason, comorbid conditions are considered confounding variables in analysis of data from clinical trials.11 Factors to take into consideration are the patient’s age, performance status, and the number of comorbid conditions.
present. Early mortality directly resulting from comorbid conditions will diminish the apparent effectiveness of a specific treatment. And the reduction in follow-up time will decrease the statistical power of the trial to detect differences between treatment and control arms.

Grading global comorbidity using single scores such as age or physical performance status first found wide appeal among those conducting clinical research. In the past, most clinical research studies of cancer treatment excluded the elderly on the basis of age, poor performance status, or the presence of abnormal laboratory studies reflecting possible visceral disease. As a result, evidence-based information for cancer treatment in the elderly is virtually nonexistent. In a recent study of Southwest Oncology Group trials conducted between 1993 and 1996, only 25 percent of patients were 65 years of age or older. In contrast, the proportion of all cancer patients diagnosed during this period was estimated at 63 percent. The percentage of clinical trial participants in this age category was significantly lower than in the overall population of patients for 14 of the 15 cancer types, the only exception being lymphoma trials. Under-representation was especially striking in breast cancer trials, with the percentage of elderly patients in the trials and in the general population being 9 percent and 49 percent, respectively.

For clinical trials in the elderly, prognostic parity is of absolute necessity. In an effort to provide retrospective descriptive information about these comorbid conditions, some investigators have sought refuge in coded administrative data sets using them as a quick and readily available solution to the quantification of comorbidity for large numbers of cancer patients. However, when conducting clinical trials, a prospective approach is generally required to assure valid answers, although some retrospective analysis may be possible.

From estimating the number of study subjects sufficient to answer particular research questions to making a valid interpretation of outcome data, study design requires greater attention in this population. The ideal situation is to have a balanced distribution of patients with concomitant medical problems in each of the experimental groups through stratification prior to randomization. Meaningful retrospective analysis of the data may be impossible if there is a distorted distribution of comorbid conditions among the study subjects between groups receiving different treatment interventions.

Including the elderly in companion protocols that examine interventions designed to minimize collateral damage from poor resilience to treatment toxicity or concomitant medical conditions is informative. Because the elderly as a group are highly sensitive to toxic treatments and have the least resiliency during recovery, methods that improve management in the elderly may also find applicability in a younger population. The expanding size of the elderly population living with cancer in the coming decades makes them an ideal source of cancer research participants.

Over the past 50 years, physical performance status has been used to contribute to an understanding of prognosis in stratified patients before they undergo experimental chemotherapy. The Karnofsky performance status score, first described in 1947, has been used extensively, as have successor summary physical performance scores such as the Eastern Cooperative Oncology Group performance status score collected during clinical trials.

Performance status has proven both reliable and valid in the hands of trained providers. It has been a mainstay for eliminating high-risk patients from clinical trials, thus improving the efficiency and accuracy of the conclusions for multi-institutional cooperative clinical research purposes.

The study of quality-of-life issues could prove critical as a research resource for marginally beneficial treatment interventions for patients of all ages but particularly for the elderly.
Prognostic parity would be enhanced if there were a reliable, valid, and efficient instrument capable of measuring comorbidity that proved readily adaptable to the design, conduct, and analysis of cancer treatment trials in the elderly. The search for the optimal instrument to measure comorbidity continues.

**MEASUREMENT OF COMORBIDITY**

One of the major difficulties in reliably collecting information about comorbid conditions is the fact that both patients and their physicians may fail to recognize or may not appreciate the importance of the condition. Elderly patients with multifaceted medical histories often receive focused attention on only their most severe, treatable problems. Even if a comorbid condition is recognized, there is a possibility its presence may go unrecorded.

Administrative data sets are totally dependent upon a series of data transfers, which may not be reliable. This information may vary from being slightly distorted to completely absent as the chain of discovery moves from the patient to the physician to the administrative record and on to the person responsible for the administrative coding (Figure 2).

One of the first formal attempts to assess the influence of comorbid disease was a retrospective review of individuals with maturity-onset diabetes mellitus. In this report the complications were classified as either vascular or non-vascular. The investigators were concerned that the interpretation of treatment outcomes might be prone to error when the accuracy of the prognostic expectations being supplemented with data regarding comorbidity could be called into question. Severity scores for comorbid conditions were assigned, and patients were grouped based on their maximum comorbidity score.

Subsequently, a weighted comorbidity index was derived from one-year mortality rates for a medical population for whom the comorbid conditions were extracted from the chart and subjected to a multivariate analysis resulting in a summary severity index. Summary comorbidity measures are appealing because they facilitate the analysis of complex comorbidity data.

With the advent of readily-accessible warehoused data sets and computers capable of analyzing massive amounts of data, investigators have pursued common definitions to assure comparability during the analytic stages. This allows more consistency in the study of treatment interventions with regard to how they relate to the impact of comorbid conditions.

These administrative databases provide convenient sources of information; however, their accuracy is highly dependent upon a chain of events that include the following: Data recognition and documentation, and the appropriate translation of that documentation into a categorical administrative code for the various comorbid conditions.

The search continues for a single value that would allow a ranking of comorbidity. The resulting summary number, comprised of the number of conditions as well as the measure of their severity, has led to an oversimplification.

Comorbidity is often measured by the Cumulative Illness Rating Scale–Geriatric (CIRS–G) or the Charlson Scale. The CIRS–G classifies comorbid conditions by organ system and grades each condition from zero to four (zero signifying no problem, four
designating severely incapacitating or life-threatening). The Charlson comorbidity scale summarizes the presence of 19 conditions, which are each weighted from one to six based on their statistical relationships to one-year mortality rates. Correlation between the two comorbidity indices in some studies has been only fair to marginal, reflecting validity problems with single-measure instruments for assessing comorbidity.18

Other comorbidity measures include the comorbidity index, the Duke Severity of Illness Checklist, the Kaplan and Feinstein measure, and the Chronic Disease Score.2,11 One might confuse comorbidity with related constructs such as performance status and functional measures, but comorbidity measures appear to be statistically independent of Eastern Cooperative Oncology Group (ECOG) performance status and functional scales such as Activities of Daily Living and Instrumental Activities of Daily Living.18 The latter summarizes patients’ ability to perform specific self-care tasks.

As noted, unrecognized and under-reported comorbid conditions in the elderly cancer population contribute to a lack of caution causing suboptimal management of these patients. Malnutrition, leading to significant weight loss, is often considered to be a part of the disease process and thus receives inadequate attention. In recent years, the use of interferon and its accompanying fatigue symptoms seldom gets recorded except as part of a reporting requirement for an experimental protocol.

Even though most oncologists appreciate the existence of anxiety and depression in this patient population, the customary documentation in administrative records may exist only in the form of a notation about medication for sleep or anxiety. The reporting and quantification of pain is often simply inferred from the medication prescribed, without explicit descriptive notations made in the provider’s office and/or hospital record. And, there is almost never any documentation addressing the level of patients’ understanding, competence, and desire to participate in their own cancer management.

Many elderly patients are dependent upon family members or friends to help them navigate an increasingly complex medical system. With complex toxic treatment interventions, this lack of knowledge and the inability to assure bi-directional communication can lead to life-threatening mistakes.

Disease denial is common for many individuals as they try to protect their privacy from friends and family. Although the elderly do not have to worry about workplace or insurance discrimination, many are concerned about unwanted pity or sympathy. This fosters personal secrecy. Each of these unappreciated findings may significantly diminish the quality of life for the elderly patient living with cancer. It is unlikely that even a small percentage of these known but underappreciated comorbidities have been or will be documented by health care providers.

In addition, documentation of episodic billing for care and medication is seldom cumulative and this encourages information deficits in the fiscal records. The administrative codes used to tabulate specific comorbid conditions are totally dependent upon that documentation. The complexity of the problem is illustrated by the under-representation of some comorbidities for similar populations of men with benign prostatic hypertrophy. After an adjustment for comorbidity based on discharge information, men having a transurethral prostatectomy had an increased five-year mortality rate when compared with those having a suprapubic prostatectomy.19,20

In a replicate study, the same results occurred until the investigators used a review of the medical records.21 They then found that the administrative data missed some of the significant comorbid conditions. However, once the data were adjusted with the newly-found comorbid conditions, the differences in five-year mortality rates for the two groups disappeared.
The seductive attraction of the efficiency, economy, and ease of application to massive data sets and the cumbersome and costly aspects of chart reviews will most likely perpetuate multiple attempts to achieve single-measure scores for comorbidity derived from administrative data.

Because it is possible to apply these methods to administrative data sets, the great potential for misleading conclusions must be appreciated. Before the practice of applying such methods is accepted as a legitimate technique to study comorbidity in the elderly patient with cancer, their validation will require hospital and providers’ office chart reviews in smaller, more manageable ways to assure complete ascertainment of the comorbid conditions.

REFERENCES

1. Feinstein A. Clinical Judgment. New York: The Williams & Wilkins Company, 1967.
2. Nitz, NM. Comorbidity. In: RL Kane, ed. Understanding Health Care Outcomes Research. Gaithersburg: Aspen; 1997:153-174.
3. Yancik R, Wesley MN, Ries LAG, et al. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. Cancer 1998;82:2123-2134.
4. Yancik R, Wesley, MN, Ries LAG, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;286:885-892.
5. Ries LAG, Eisner MP, Hankey BE et. al. SEER Cancer Statistics Review, 1973-1998: National Cancer Institute, 2001.
6. Yancik R, Kesler I, Yates JW. The elderly population: opportunities for cancer prevention and detection. Cancer 1988;62:1823-1828.
7. Lichtman SM, Skirvin JA. Pharmacology of antineoplastic agents in older cancer patients. Oncology 2000;14:1743-1759.
8. Wells NL, Baldacci L. Geriatric Oncology: Medical and psychosocial perspectives. Cancer Practice 1997;5:87-91.
9. Reuben DB. Geriatric assessment in oncology. Cancer 1997;80:1311-1316.
10. Hutchins LF, Unger MS, Crowley JJ, et al. Under-representation of patients 65 years of age or older in cancer-treatment trials. New Engl J Med 1999;341:2061-2067.
11. Schneeweis S, McHure M. Use of comorbidity scores for control of confounding in studies using administrative databases. Int J Epidemiol 2000;5:891-898.
12. Charlson ME, Sax FL, MacKenzie CR, et al. Assessing illness severity: Does clinical judgment work? J Chron Dis 1986;39:439-452.
13. Charlson ME, Pompei P, Alex KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis 1987;40:373-383.
14. Yates JW, Chalmer B, McKegney FP. Evaluations of patients with advanced cancer using the Karnofsky Performance Status. Cancer 1980;45:2220-2224.
15. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: An examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.
16. Zubrod CG, Schneiderman M, Frei E, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiolethylene thiophosphoramide. J Chronic Dis 1960;11:7-33.
17. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387-404.
18. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998;16:1582-1587.
19. Roos N, Wendberg JE, Malenka DJ, et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med 1989;320:1120-1124.
20. Malenka DJ, Roos N, Fisher ES, et al. Further study of the increased mortality following transurethral prostatectomy; a chart based analyses. J Urol 1990;144:224-228.
21. Concato J, Horwitz RI, Feinstein AR, et al. Problems of comorbidity in mortality after prostatectomy. JAMA 1992;267:1077-1082.