The Impact of Chronic Illnesses on the Use and Effectiveness of Adjuvant Chemotherapy for Colon Cancer

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Cary P. Gross was supported by a Beeson Career Development Award (1 K08 AG24842) and by the Claude D. Pepper Older Americans Independence Center at Yale (P30AG21342).

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Received December 13, 2006; revision received March 7, 2007; accepted March 9, 2007.

BACKGROUND. It is unclear how noncancer conditions affect the use or effectiveness of adjuvant therapy among older patients with colon cancer.

METHODS. The authors conducted a cohort study of older patients with stage III colon cancer who were diagnosed from 1993 to 1999 in the Surveillance, Epidemiology, and End Results-Medicare database. The correlations between receipt of adjuvant chemotherapy and heart failure, diabetes, and chronic obstructive pulmonary disease (COPD) were assessed. Multivariable regression analysis was used to assess the risk of death and hospitalization as a function of treatment and comorbidity status.

RESULTS. The study sample consisted of 5330 patients (median age, 76 years). The use of adjuvant therapy was related significantly to heart failure (36.2% vs 64.9% of patients with vs without heart failure, respectively; adjusted odds ratio [OR], 0.49; 95% confidence interval [95% CI], 0.40–0.60). More moderate correlations were observed for COPD (OR, 0.83; 95% CI, 0.70–0.99) and diabetes (OR, 0.81; 95% CI, 0.68–0.97). Among patients who had heart failure, the 5-year survival was significantly higher among those who received adjuvant chemotherapy (adjusted 5-year survival rate, 43%; 95% CI, 40–47%) than among those who did not receive adjuvant chemotherapy (30%; 95% CI, 27–34%). Among patients without heart failure, the 5-year survival estimates among treated and untreated patients were 54% (95% CI, 52–56%) and 41% (95% CI, 38–44%), respectively. The probability of all-cause, condition-specific, or toxicity-related hospitalization associated with adjuvant therapy was not altered by the presence of any of the 3 conditions.

CONCLUSIONS. Although chronic conditions appeared to be a strong barrier to the receipt of adjuvant chemotherapy, adjuvant therapy appeared to provide a significant survival benefit to patients who had colon cancer with the conditions studied. ***Cancer* 2007;109:2410–9.** © *2007 American Cancer Society.*

KEYWORDS: aging, geriatrics, comorbidity, multimorbidity, colon cancer, adjuvant therapy.

Older individuals bear the greatest burden of colon cancer. Currently, the median age at diagnosis for patients with colon cancer is >70 years, and most patients in this age group have ≥4 different chronic conditions.[1–3] These chronic conditions have a substantial impact, because patients with a greater burden of comorbidity are less likely to survive after a cancer diagnosis.[1–5] However, prior work has tended to aggregate chronic conditions into a *comorbidity index* with little consideration of how specific conditions affect patterns of care or outcomes among older patients with cancer.

DOI 10.1002/cncr.22726
Published online 17 May 2007 in Wiley InterScience (www.interscience.wiley.com).

One important decision facing patients with stage III colon cancer and their clinicians concerns the use of adjuvant chemotherapy. Evidence from clinical trials suggests that adjuvant chemotherapy is associated with a 34% reduction in mortality, and population-based observational studies have demonstrated similar survival benefits.[6–8] Prior work also has suggested that the survival benefits associated with adjuvant therapy do not diminish with increasing age.[8,9] However, those findings stand in stark contrast to current patterns of care, in which increasing age is associated inversely with the receipt of adjuvant therapy.[10–13] It has been reported that the use of adjuvant therapy decreases from approximately 75% of patients ages 65 years to 80 years to <40% of patients aged >80 years.[7,9,14]

To understand the use and effectiveness of adjuvant therapy in older patients with colon cancer, it is imperative to increase our understanding of how they are affected by noncancer illnesses. The typical older oncology patient has at least 3 noncancer conditions, and the prevalence of these conditions increases with age.[3] Although patients with a higher number of conditions tend to receive adjuvant therapy less frequently, it is unclear whether specific conditions affect the probability of receiving adjuvant therapy or the risks and benefits of treatment.[9,13] Some authors have called for further evidence to help guide clinical decision-making in this area.[8] Although it is possible that comorbid conditions increase the risk of toxicity-related hospitalizations, this has not been investigated to our knowledge.[9] In addition, it is unclear whether adjuvant therapy increases the risk of hospitalizations related to exacerbations of the underlying chronic illnesses.

We conducted a population-based study of older patients with stage III colon cancer to gain a further understanding of the relation between specific, common comorbid conditions and adjuvant chemotherapy use. Specifically, we determined the degree to which specific conditions affected the probability of receiving adjuvant chemotherapy from 1995 to 1999 as well as the risks and benefits of therapy.

MATERIALS AND METHODS

Construction of the Study Sample

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database is a population-based tumor registry that has been linked with Medicare administrative claims data.[15,16] Patient-level information available from SEER includes sociodemographic characteristics, cancer type, site, histologic grade, and disease stage.[17] Patients aged ≥67 years who were diagnosed with primary adenocarcinoma of the colon from 1993 to 1999 were included in the current analysis. This age was selected to allow for 2 years of Medicare eligibility and administrative claims for all patients. Additional patients were excluded if their date of death was recorded as prior to or the same month as the month of their cancer diagnosis (n = 1446 patients), if the data source was autopsy or death certificate (n = 120 patients), or if they had missing information regarding their race (n = 115 patients). Patients were also excluded if they were ineligible for Medicare Part A and B coverage (n = 2749 patients) or fee-for-service coverage (n = 9226 patients) during the 2-year period prior to their cancer diagnosis, because these services are not included in Medicare clams files. Of the 28,733 patients with colon cancer who fulfilled these criteria, 6637 patients had stage III colon cancer, and 5490 patients had lived for ≥6 months after their diagnosis and had undergone resection during that time. Consistent with prior studies of adjuvant chemotherapy use, we also excluded patients who had not received chemotherapy and had died within 6 months of surgery, because we wanted to restrict our sample to patients who did not have a short-term prognosis that was so poor that it would preclude their consideration for adjuvant therapy.[9] We also excluded 27 patients who had no lymph nodes that were positive for malignancy, leaving a sample size of 5330. Patients may have had more than 1 reason for exclusion.

Construction of Variables

Comorbid conditions that comprised the Charlson comorbidity index as well as additional conditions that were selected according to clinical judgment were identified by searching inpatient, outpatient, and physician claims using a modification of a previously specified algorithm.[18,19] The claims from 2 years prior to cancer diagnosis to 30 days afterward diagnosis were searched for each patient to identify the specific comorbid conditions of interest. Treatment-related variables, such as cancer-specific surgery and chemotherapy, were identified by searching patient claims using previously validated approaches.[8,12,20,21] Consistent with prior work, we defined *completing* a course of adjuvant therapy as having at least 1 claim for chemotherapy administration during 5 of 6 consecutive months beginning with the initial claim.[22]

Condition-related hospitalizations were defined as hospitalizations with a primary diagnosis code for 1 of the 3 conditions using a previously validated approach.[23] For instance, patients with chronic obstructive pulmonary disease (COPD) were categor-

ized according to whether they were hospitalized with an International Classification of Diseases (ICD) code consistent with a principal diagnosis of COPD. Admissions related to acute diabetes complications were too rare to include in the analysis. Adjuvant chemotherapy-related toxicity has been associated with specific complications, some of which require hospitalization.[9,24] Hospital admissions that potentially were the result of toxicity were identified by searching admission claims for ICD (9th revision) codes consistent with infection (infection, fever, septicemia, or bacteremia), hematologic toxicity (anemia, thrombocytopenia, neutropenia), or gastrointestinal (GI)/other toxicity (nausea or vomiting, dehydration, diarrhea, stomatitis, or adverse effects of systemic therapy), as reported previously.[25,26] Because these diagnoses are nonspecific, we defined toxicity-attributable hospitalizations as the difference in the proportion of treated and untreated patients who were admitted with 1 of these infectious/hematologic/GI diagnoses.

Analysis

We decided a priori to determine whether the use and effectiveness of adjuvant chemotherapy was moderated by any of the 3 most common conditions in our cohort.[27] These conditions were congestive heart failure (CHF), COPD, and diabetes. First, we identified the factors associated with use of adjuvant therapy in bivariate analysis. Based on clinical judgment and prior literature, we investigated comorbid conditions, year of diagnosis, patient age, race (white, black, other), marital status, urban/rural designation, SEER site, median income (by zip code), and cancer-specific information, such as histologic grade, number of lymph nodes positive for carcinoma, and tumor site (proximal colon vs distal colon). The total number of physician visits and the number of hospitalizations during the 2 years prior to cancer diagnosis also were included. Significant variables were entered into a multivariate logistic regression model to identify that factors that were associated independently with receiving chemotherapy and, for patients who had initiated therapy, with completing chemotherapy. The models were evaluated extensively by examining deviance, Pearson, and Hosmer & Lemeshow goodness-of-fit statistics. There were 193 patients (3.6%) with missing data on income. We did multiple imputation with 50 random draws per missing observation and replaced the missing value with the mean of the 50 imputed values.[27]

Effectiveness

We used propensity scores to control for bias when comparing outcomes of treated and untreated patients. Propensity scores represent the probability of receiving a treatment for an individual with specific characteristics.[29] By incorporating all known and measured confounders of the relation between treatment and outcome, propensity scores allow investigators to compare treated and untreated patients after balancing the distribution of these background covariates.[29,30] Because different approaches for using propensity scores offer unique strengths and limitations, we decided a priori to use 2 approaches to determine whether our findings would be robust.

In the first approach, we estimated the propensity score for each patient by using a logistic regression model that included the individual covariates listed in Table 1 as well as SEER registry, year of diagnosis, residence in an urban location versus a rural location, and median income (by zip code). Then, the effect of chemotherapy on mortality was examined using a Cox proportional-hazards model that included the propensity score as a predictor variable. We also included treatment status and each of the 3 chronic conditions in the model and then examined whether there was an interaction between chemotherapy and each condition (eg, CHF and chemotherapy). Survival was calculated as the time from diagnosis until death or December 31, 2002, whichever occurred first; deaths from all causes were counted as failures. The proportional-hazards assumption was assessed by plotting log-negative/log-survival function over log of time and Shoenfeld residuals over time. Then, we calculated the predicted survival according to chemotherapy status after stratifying according to the presence or absence of each comorbid condition and the setting propensity score to the sample mean.

The second approach involved matching patients by propensity score. Because patients with chronic conditions are less likely to receive treatment, we were concerned that the relation between covariates and receipt of adjuvant therapy might be different according to comorbidity status. Therefore, as a complement to our first approach in which the full sample was evaluated in single pool, we also recalculated the propensity score in each chronic condition group. We then used the propensity score to match each treated patient with an untreated patient.[31] For example, we were able to match 1037 pairs (with and without chemotherapy) of patients without CHF and 217 pairs of patients with CHF. Then, we re-estimated the survival model in each group. We repeated the analysis after stratifying the *chemotherapy* vari-

TABLE 1
Patient Characteristics and Receipt of Adjuvant Chemotherapy

Patient characteristic	No.	%	% Receiving adjuvant chemotherapy	*P*	Patient characteristic	No.	%	% Receiving adjuvant chemotherapy	*P*
Age group				<.001	Ulcer				<.001
67–70	971	18.2	83.8		No	5059	94.9	60.8	
71–75	1442	27.1	78.2		Yes	271	5.1	50.2	
76–80	1330	25.0	63.1		Peripheral vascular disease				<.001
81–85	938	17.6	37.6		No	5010	94.0	60.9	
86 or older	649	12.2	10.9		Yes	320	6.0	51.3	
Sex				<.001	Rheumatologic disease				.14
Men	2161	40.5	66.1		No	5211	97.8	60.4	
Women	3169	59.5	56.3		Yes	119	2.2	53.8	
Race				.075	Paralysis				<.001
White	4636	87.0	60.6		No	5245	98.4	60.8	
Black	394	7.4	55.1		Yes	85	1.6	25.9	
Others	300	5.6	62.3		Chronic renal failure				.012
Marital status				<.001	No	5258	98.6	60.5	
No Data	86	1.6	48.8		Yes	72	1.4	41.7	
Unmarried	2515	47.2	49.2		Hip fracture				<.001
Married	2729	51.2	70.8		No	5041	94.6	61.6	
Cancer site				.36	Yes	289	5.4	37.7	
Proximal Colon	3583	67.2	59.6		Dementia				<001
Distal Colon	1675	31.4	61.5		No	5192	97.4	61.5	
Colon NOS	72	1.4	63.9		Yes	138	2.6	15.2	
Positive lymph nodes				<.001	Cerebrovascular disease				<.001
1–3	3677	69.0	57.9		No	4858	91.1	61.9	
4–7	1111	20.8	65.1		Yes	472	8.9	43.2	
8 or more	397	7.4	70.5		Atrial fibrillation				<.001
Unknown	145	2.7	56.6		No	4519	84.8	63.3	
Total no. of conditions				<.001	Yes	811	15.2	43.6	
0	2479	46.5	69.1		Venous thromboembolism				.001
1–2	2380	44.7	55.4		No	5187	97.1	60.7	
3 or more	471	8.8	38.6		Yes	152	2.9	47.4	
Heart failure				<.001	Prior physician visits				<.001
No	4477	84.0	64.9		0–1	613	11.5	55.0	
Yes	853	16.0	36.2		2–5	1061	19.9	65.2	
Diabetes				.17	6–9	1083	20.3	60.9	
No	4380	82.2	60.7		10–14	1021	19.2	62.1	
Yes	950	17.8	58.3		15 or more	1552	29.1	57.3	
COPD				<.001	Previous hospital days				<.001
No	4326	81.2	61.5		0	3975	74.6	64.2	
Yes	1004	18.8	55.2		1–2	223	4.2	60.5	
Liver disease				.075	3–5	405	7.6	52.6	
No	5269	98.9	60.4		6–10	360	6.8	48.1	
Yes	61	1.1	49.2		11 or more	367	6.9	38.7	
Myocardial infarction				< .001					
No	4934	92.6	61.2						
Yes	396	7.4	48.5						

Prior physician visits and Previous hospital days reflect the number of each that occurred during the period 24 months through 2 months before cancer diagnosis.

able into categories of *completed therapy* or *incomplete therapy.* Because our inferences did not change when we analyzed the data in this manner, only the primary analyses are presented herein.

Bivariate analysis was used to compare the frequency of each of the 3 types of hospitalizations according to chronic illness and treatment status using the chi-square test. We then examined the independent association between treatment status and toxicity-related hospitalizations using multivariable logistic regression models stratified by chronic condition status. We also looked at combinations of the 3 conditions by creating a summary variable (total number of conditions). Because the total number of

TABLE 2
Initiation and Completion of Adjuvant Chemotherapy According to Chronic Condition Status

Chronic condition	Initiation of chemotherapy 5330 patients eligible			Completion of chemotherapy, if initiated 3213 patients eligible		
		Adjusted odds ratio			Adjusted odds ratio	
	%	OR (95%CI)	*P*	%	OR (95%CI)	*P*
(–) CHF	64.9	1	<.001	74.6	1	.11
(+) CHF	36.2	0.49 (0.40–0.60)		66.0	0.79 (0.60–1.06)	
(–) COPD	61.5	1	.04	74.5	1	.05
(+) COPD	55.2	0.83 (0.70–0.99)		70.0	0.80 (0.65–1.00)	
(–) Diabetes	60.7	1	.02	74.2	1	.17
(+) Diabetes	58.3	0.81 (0.68–0.97)		71.5	0.86 (0.69–1.07)	

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease.
Odds ratios adjusted for sociodemographic factors, comorbid conditions, cancer characteristics, SEER registry, year of diagnosis, urban verus rural location, hospitalizations, and physician visits before cancer diagnosis.

conditions was not related significantly to toxicity-related hospitalizations for patients who received chemotherapy, the results from combinations of conditions are not presented. All statistical tests were 2-tailed, and all analyses were performed using SAS software (version 9.1).[32]

RESULTS

The final study sample consisted of 5330 patients, and 60.3% of those patients had received adjuvant therapy. Approximately 59.5% of the patients were women, 87% were white, and the median age was 76 years. Increasing age was related inversely to the probability of receiving chemotherapy in addition to being a woman, the total number of comorbid conditions, and being unmarried at the time of cancer diagnosis (Table 1). Overall, approximately 46.5% of the study sample had no claims consistent with comorbid conditions, 44.7% had 1 or 2 conditions, and 8.8% had $\geq$3 conditions. The total number of chronic conditions was related strongly to the receipt of chemotherapy, Overall, 69.1% of patients with no conditions and 38.6% of patients with $\geq$3 conditions received treatment.

The most common comorbid conditions in the study cohort included heart failure (16%), COPD (18.8%), and diabetes (17.8%). The receipt of adjuvant therapy was related significantly to heart failure (36.2% vs 64.9% of patients with vs without heart failure, respectively, adjusted odds ratio [OR], 0.49; 95% confidence interval [95% CI], 0.40–0.60). More moderate relations were observed for COPD (55.2% vs 61.5% of patients with vs without COPD, respectively; OR, 0.83; 95% CI, 0.70–0.99) and diabetes (58.3% vs 60.7% of patients with vs without diabetes, respectively; OR, 0.81; 95% CI, 0.68–0.97). Among the patients who started chemotherapy, there was not a consistent relation between having the chronic conditions and completing the regimen (Table 2).

Effectiveness

The median survival was 4 years, and 3166 patients died (59.4%) during follow-up. The maximum follow-up was 10 years. Adjuvant therapy was associated with a significant reduction in mortality (hazard ratio [HR], 0.70; 95% CI, 0.64–0.76) after adjusting for sociodemographic and clinical characteristics using propensity scores. Patients who received chemotherapy and did not have heart failure had the highest survival probability, whereas patients who did not receive chemotherapy and did have CHF had the lowest probability of survival (Fig. 1, left). However, it is noteworthy that the difference in survival curves between treated and untreated patients was similar for patients with and without CHF. For instance, among patients who had CHF, the 5-year survival probability was 43% (95% CI, 40–47%) if they received chemotherapy compared with 30% (95% CI, 27–34%) among patients who did not receive chemotherapy. Similarly, among patients without CHF, the 5-year survival was estimated at 54% (95% CI, 52–56%) among patients who received chemotherapy compared with 41% (95% CI, 38–44%) among patients who did not receive chemotherapy. This survival benefit associated with chemotherapy was consistent across time and also was demonstrated after stratifying by COPD and diabetes status (Fig. 1, middle and right, respectively). Treated patients had a higher 5-year survival than untreated patients for all groups, including patients who had COPD (46.2% vs 32.9%, respectively, for treated vs untreated patients) or diabetes (47.4% vs 34.1%, respectively).

When we repeated the analysis after stratifying patients according to chronic disease status and then matching them by propensity score, the results were similar. Among the 2074 patients without CHF, the HR for mortality associated with chemotherapy use was 0.67 (95% CI, 0.60–0.75) (Fig. 2). Among the patients with CHF, adjuvant chemotherapy use was associated with an HR of 0.70 (95% CI, 0.56–0.87). The findings were similar after stratifying by diabetes and COPD status and by the total number of chronic conditions (Fig. 2).

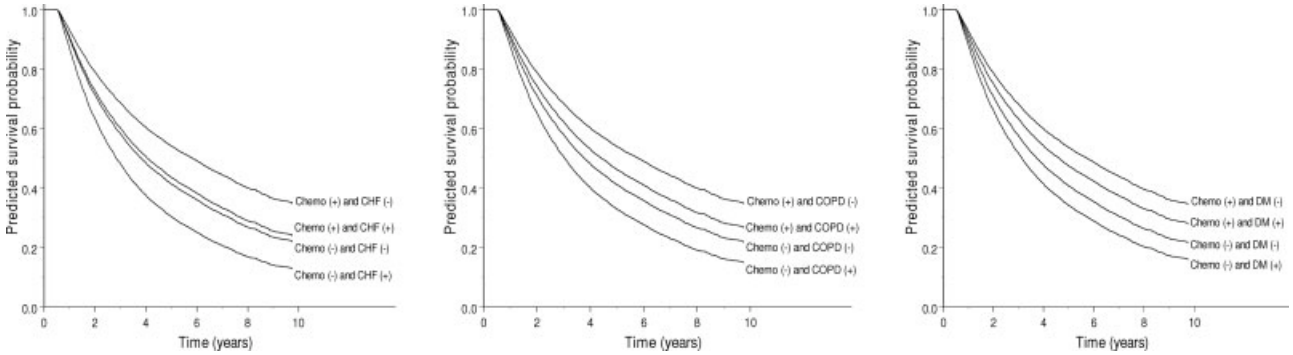

FIGURE 1. Predicted survival probability over time according to treatment status and chronic conditions. Adjusted survival estimates were obtained with a Cox proportional-hazards model based on the sample mean of the propensity score from a logistic regression model that included sociodemographic factors; comorbid conditions; cancer characteristics; Surveillance, Epidemiology, and End Results registry; year of diagnosis; and urban versus rural location. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; chemo, adjuvant chemotherapy.

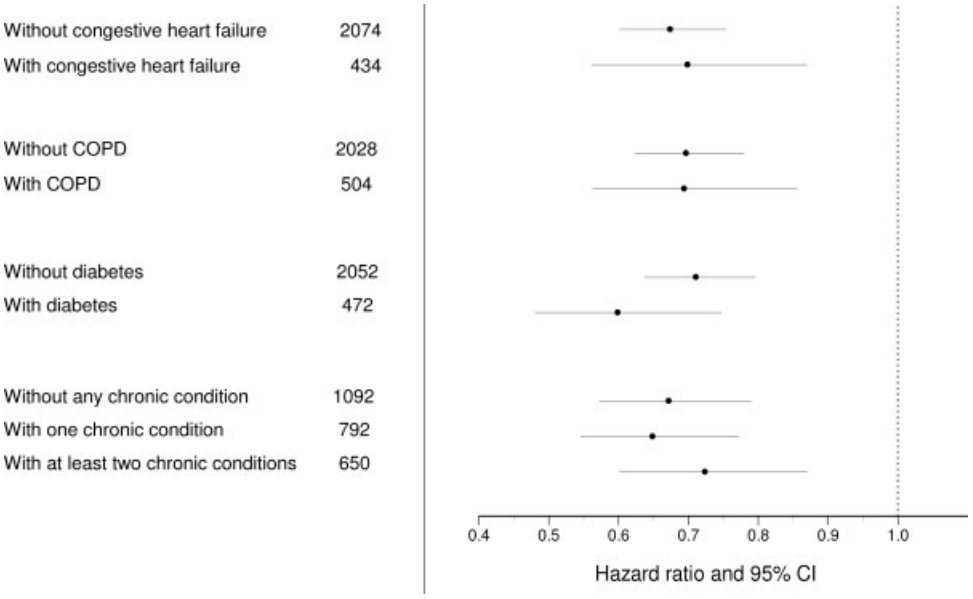

FIGURE 2. Effect of adjuvant therapy on mortality according to chronic disease status. Dots and lines represent the hazard ratio of death and its 95% confidence interval (95% CI) in relation to chemotherapy use in each sample. Numbers represent the numbers of cancer patients (sample size) after matching (by propensity score) between patients who did and did not receive chemotherapy in each chronic illness stratum. COPD indicates chronic obstructive pulmonary disease.

Hospitalizations

Among the patients with heart failure, the probability of having any hospitalization during the year after cancer surgery was similar for patients who received adjuvant therapy (54.7% 95% CI, 49.0–60.3%) and for patients who did not receive adjuvant therapy (52.4%; 95% CI: 48.1–56.6%) (Fig. 3). These findings persisted after adjusting for sociodemographic and clinical factors (adjusted OR for hospitalization for CHF patients who received adjuvant therapy vs untreated patients: 1.06; 95% CI, 0.75–1.50). Similarly, the receipt of adjuvant therapy was not associated with an increased probability of all-cause hospitalization for patients with COPD or diabetes (adjusted $P = .48$ and $P = .85$, respectively). The probability of condition-specific hospitalizations for patients with CHF or COPD also was not related significantly to treatment status (Fig. 3B). Among patients with CHF, for instance, approximately 7.1% (95% CI, 4.5–10.6%) of treated patients and 8.8% (95% CI, 6.6–11.5%) of untreated patients were admitted with a CHF exacerbation ($P = .80$ in the multivariate model).

Patients with chronic conditions were more likely than patients without chronic conditions to be hospitalized with GI, hematologic, or infectious diagnoses after their surgery. Among patients who received adjuvant therapy, 8.8% of patients without CHF (95% CI, 6.3–11.4%) compared with 5.4% of patients with CHF (−1.1–12%) experienced a hospitalization that was attributable to chemotherapy toxicity (Table 3). In multivariate analysis, chemotherapy increased the odds of GI/hematologic/infec-

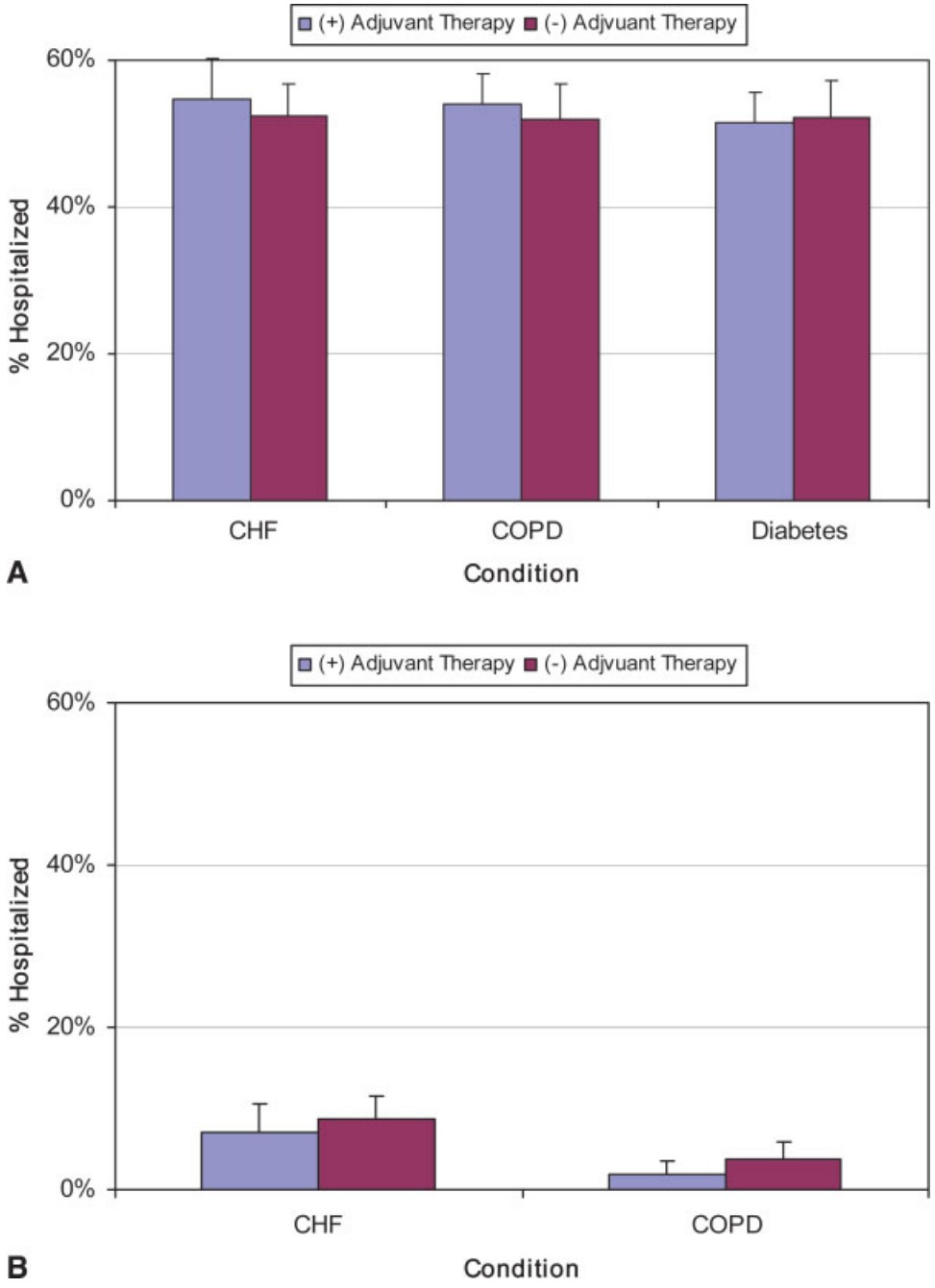

FIGURE 3. (A) All-cause hospitalizations according to treatment status for patients with chronic conditions. (B) Condition-specific hospitalizations according to treatment status for patients with chronic conditions. The percentages of patients who experienced (A) all-cause and (B) condition-specific hospitalizations during the year after surgery are illustrated according to treatment and chronic condition status. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease.

tious hospitalization for patients without CHF, but not for patients with CHF (adjusted odds for treated vs untreated patients: 1.92 [95% CI, 1.60–2.30] and 1.20 [95% CI, 0.82–1.73], respectively). The interaction between chemotherapy and CHF was of borderline significance ($P = .07$), suggesting that chemotherapy may increase the risk of chemotherapy-related toxicity in CHF patients to a lesser degree that it does in patients without CHF. There were no significant interactions between either COPD or diabetes and adjuvant therapy, suggesting that the receipt of therapy increased the risk of toxicity-related hospitalization to the same degree in patients with and without these conditions (Table 3).

DISCUSSION

The current study builds on our prior work, which demonstrated that patients with an increasing number of chronic conditions were less likely to receive

TABLE 3
Hospitalization with Gastrointestinal, Hematologic, or Infectious Diagnosis According to Treatment and Chronic Illness Status

	% of patients hospitalized		Hospitalizations attributable to chemotherapy		*P* for interaction
	Without adjuvant therapy	With adjuvant therapy	Absolute difference in % hospitalized (treated vs untreated)	Adjusted odds ratio for hospitalization* (treated vs untreated)	Condition × therapy
Heart failure					.07
No	19.5	28.3	8.8 (6.3–11.4)	1.92 (1.60–2.30)	
Yes	28.9	34.3	5.4 (−1.1–12.0)	1.20 (0.82–1.73)	
COPD					.37
No	20.8	27.6	6.8 (4.2–9.4)	1.78 (1.49–2.14)	
Yes	26.0	35.0	9.0 (3.3–14.7)	1.61 (1.13–2.27)	
Diabetes					.35
No	21.0	28.7	7.7 (5.1–10.3)	1.80 (1.51–2.16)	
Yes	26.0	30.1	4.1 (−1.6–9.9)	1.67 (1.16–2.41)	

COPD indicates chronic obstructive pulmonary disease.

* Adjusted odds of hospitalization with an ICD-9 code consistent with gastrointestinal (GI), hematological, or infection-related diagnosis for chemotherapy-treated versus. untreated patients in each row. Adjusted for age, gender, race, gender, income in patient zip code area, year of diagnosis, marital status, urban/rural setting, cancer grade, site, number of positive lymph nodes, SEER registry, number of physician visits, days spent hospitalized before cancer diagnosis, and other comorbid conditions.

adjuvant therapy. We observed that individual conditions varied in their relation to the use and outcomes associated with treatment. Patients with heart failure were <50% as likely as patients without heart failure to receive adjuvant therapy after the underwent surgical resection for colon cancer, whereas COPD had a modest relation and diabetes had little impact on receipt of therapy. This emphasizes the importance of moving beyond a *comorbidity index* when investigating the care and outcomes of older cancer patients. Simply counting the number of conditions with which each patient has been diagnosed may overlook important distinctions between conditions.

The inverse relation between CHF and adjuvant therapy use may be a result of the clinical concern that preexisting cardiac disease can alter the balance between risks and benefits of adjuvant treatment.[33,34] Our results do not support this concern. We observed, for example, that the relative reduction in the risk of mortality associated with adjuvant chemotherapy was similar in patients with and without CHF. In addition, the difference in adjusted 5-year survival associated with adjuvant therapy was even more favorable among patients with CHF (43% vs 29% for treated and untreated patients, respectively) than for patients without CHF (54% v. 41%, respectively). The findings were consistent for the other chronic conditions we investigated and for the total number of conditions. We also observed that CHF was not associated significantly with decreased odds of completing chemotherapy after controlling for the other covariates Thus, although comorbidity was associated with an increased risk of death, it did not diminish the relative survival benefit associated with treatment. Furthermore, adjuvant therapy was not associated with increased all-cause, condition-specific, or toxicity-related hospitalization rates for patients with the chronic conditions of interest.

Because we were only able to account for measured confounders, treatment assignment bias may account for some of the survival benefit attributed to adjuvant therapy. That is, patients with CHF who received treatment may have represented the healthiest subset of CHF patients, and this baseline difference may affect inferences about effectiveness. Therefore, it is reassuring that our overall findings (adjusted HR, 0.70) are consistent with those of prior observational studies (HR, 0.66-.073) and with the results from a pooled analysis of clinical trial data.[7,8] This reinforces prior quantitative analyses, which demonstrated that well-designed observational studies can yield estimates of treatment effectiveness that are similar to those reported in randomized trials.[35–37] We also employed additional, novel approaches to account for bias. To capture health status, we adjusted for prior hospitalizations and physician visits. Furthermore, unlike most prior analyses, we employed complementary approaches, using matching (by propensity score) and adjusting (for propensity score) to analyze treatment effectiveness within clinical subgroups. Our separate matching strategy assured that all covariates in Table 1 were well balanced between treated and untreated patients among those with and without the 3 chronic conditions. Our findings were consistent across both approaches. Finally, because our sample was re-

stricted to patients who had undergone surgery, patients with more severe CHF or COPD may have been excluded from the sample on the basis of their poor surgical risk. Hence, the patients in our sample may represent a relatively healthy subgroup of patients with these conditions.

It is important to recognize that administrative data do not capture all clinical diagnoses of chronic conditions, nor do they capture all outcomes that are of interest to patients, including potential chemotherapy toxicities. In addition, SEER-Medicare data may not distinguish reliably between cancer- and noncancer-related outcomes, such as death or hospitalization. Also, our study period (the late 1990s) was immediately prior to the availability of newer agents, such as capecitabine and oxiplatin, with varying risk, benefit, and cost profiles.[38–40] Hence, 5-flourourocil still was the standard of care for patients in our cohort.[20,22] Clinical decision-making will be facilitated by a greater understanding of the harms and benefits of newer agents across a spectrum of patients, including those with comorbidities, as the portfolio of treatment options expands.

We have observed that chronic conditions may affect patterns of cancer care in a manner that does not reflect their relation to clinical effectiveness. This discrepancy between effectiveness and utilization may reflect the lack of available data, because clinicians and patients need to know how the balance between harms and benefits of a proposed cancer treatment are by altered noncancer conditions. Unfortunately, the recent emphasis on increasing the representation of elderly patients with comorbid conditions into clinical trials has had meager success to date.[41–44] Future work should include prospective studies that have patient-reported outcome measures, such as quality of life, symptom burden, and functional status, with a focus on determining whether these are affected positively or negatively by treatment in patients with comorbid conditions. Because multimorbidity increasingly is the norm among patients with cancer, physicians and patients need access to the data required to make informed and appropriate treatment decisions.

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