# Multimorbidity and Survival in Older Persons with Colorectal Cancer

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**OBJECTIVES:** To ascertain the effect of common chronic conditions on mortality in older persons with colorectal cancer.

**DESIGN:** Retrospective cohort study.

**SETTING:** Population-based cancer registry.

**PARTICIPANTS:** Patients in the Surveillance Epidemiology and End Results–Medicare linked database who were aged 67 and older and had a primary diagnosis of Stage 1 to 3 colorectal cancer during 1993 through 1999.

**MEASUREMENTS:** Chronic conditions were identified using claims data, and vital status was determined from the Medicare enrollment files. After estimating the adjusted hazard ratios for mortality associated with each condition using a Cox model, the population attributable risk (PAR) was calculated for the full sample and by age subgroup.

**RESULTS:** The study sample consisted of 29,733 patients, 88% of whom were white and 55% were female. Approximately 9% of deaths were attributable to congestive heart failure (CHF; PAR = 9.4%, 95% confidence interval (CI) = 8.4–10.5%), more than 5% were attributable to chronic obstructive pulmonary disease (COPD; PAR = 5.3%, 95% CI = 4.7–6.6%), and nearly 4% were attributable to diabetes mellitus (PAR = 3.9%, 95% CI = 3.1–4.8%). The PAR associated with CHF increased with age, from 6.3% (95% CI = 4.4–8.8%) in patients aged 67 to 70 to 14.5% (95% CI = 12.0–17.5%) in patients aged 81 to 85. Multiple conditions were common. More than half of the patients who had CHF also had diabetes mellitus or COPD. The PAR associated with CHF alone (4.29%, 95% CI = 3.68–4.94%) was similar to the PAR for CHF in combination with diabetes mellitus (3.08, 95% CI = 2.60–3.61%) or COPD (3.93, 95% CI = 3.41–4.54%).

**CONCLUSION:** A substantial proportion of deaths in older persons with colorectal cancer can be attributed to CHF, diabetes mellitus, and COPD. Multimorbidity is common and exerts a substantial effect on colorectal cancer survival. **J Am Geriatr Soc 54:1898–1904, 2006.**

**Key words: cancer; epidemiology; geriatrics; comorbidity; multimorbidity**

The occurrence of multiple diseases in an individual person has been conceptualized as multimorbidity.[1,2] This represents a paradigm shift from the term comorbidity, in which a single disease is considered as of paramount importance and other conditions are secondary.[1] The recognition that disease-specific guidelines and financial performance incentives that reward compartmentalization of clinical care into discrete disease categories can have unintended consequences has fueled this paradigm shift. Oversimplification of the complex interrelation of treatment risks and benefits can lead to overtreatment and a heightened possibly of patient harm.[3,4] There has been a call for further research to clarify specific combinations of conditions that adversely affect older persons and to understand the mechanism by which conditions affect patients.[5–7]

Multimorbidity is a particularly important consideration for patients with colorectal cancer. Because more than two-thirds of patients diagnosed with colorectal cancer are aged 65 and older, and the median number of chronic conditions in colorectal cancer patients in this age group is four; multimorbidity is the norm rather than the exception.[8–10] Because multimorbidity exerts a strong effect on the probability of survival after a cancer diagnosis, there have been calls for greater understanding of how chronic conditions affect outcomes in patients with cancer.[8,11,12] It has also been suggested that a comprehensive assessment of noncancer conditions should be incorporated into a standard approach to all older persons with cancer, to facilitate an individualized approach to their care.[13] However, a lack of understanding of the degree to which specific conditions contribute to mortality risk has hampered efforts to improve the care and outcomes of older persons with cancer. A quantitative assessment of deaths attributable to readily identifiable noncancer conditions would not only facilitate risk stratification at the bedside but would also identify

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vulnerable populations for subsequent intervention research.

Critical knowledge gaps about multimorbidity remain. It is unclear how combinations of conditions and age may interact to increase mortality risk in persons with cancer. Greater clarity about the relationship between age and the burden imposed by specific conditions would not only further our understanding of why older cancer patients tend to have worse outcomes, but would also help to identify clinical entities that are likely to be increasingly common, and therefore deleterious at the population level, as the population ages. Additionally, although some research has suggested that specific combinations of conditions may be particularly deleterious to cancer patients, it is unclear how frequently these combinations occur or the degree to which they contribute to mortality risk.[14,15] Hence, authors have recently called for more empirical investigation of how multiple coexisting conditions affect cancer outcomes.[9,16]

Another important knowledge gap is the mechanism through which multimorbidity affects outcomes in patients with cancer. Prior studies have suggested that patients with a higher number of noncancer conditions are less likely to receive anticancer therapy,[17,18] but multimorbidity could affect cancer patients independently of cancer treatment. Further analyses are needed to determine to what extent receipt of cancer therapy mediates the relationship between multimorbidity and cancer mortality.

To address these knowledge gaps, a population-based study was conducted to ascertain the effect of chronic conditions on mortality in a cohort of older persons with colorectal cancer. The excess risk of death and the proportion of all deaths that were attributable to each condition were estimated. The three conditions with the highest population attributable risks (PARs) were also selected, and the variation in PAR was determined according to age groups, as well as the PARs for the combinations of these conditions. Finally, whether the risk of death associated with the conditions was changed after accounting for receipt of cancer therapy was determined.

## METHODS

A retrospective cohort study of older persons diagnosed with Stage 1 through 3 colorectal cancer was conducted to determine the proportion of deaths that were attributable to specific conditions. Patients with Stage 4 cancer were excluded, because it was hypothesized a priori that their mortality risk would be high regardless of the presence or absence of other conditions.[19,20] Patient level data were obtained from the Surveillance Epidemiology and End Results (SEER)–Medicare database.[21] All incident cases of invasive colorectal cancer reported to the SEER registries during 1993 through 1999 were cross-matched with a master file of Medicare claims through 2002.

### Study Sample

From 1993 through 1999, 55,399 people aged 67 and older were diagnosed with malignant adenocarcinoma of the colon or rectum. Sixty-seven was selected as the cutoff to ensure that each patient would have at least 2 years of Medicare eligibility (and claims) before their cancer diagnosis. Patients were excluded from the analysis if their date of death was recorded as before or in the same month as the date of their cancer diagnosis (n = 1,753); if the data source was autopsy or death certificate (139); or if they had missing information regarding their race (155), marital status (792) or socioeconomic status (1,130). Patients were also excluded if, during the 2-year period before their cancer diagnosis, they were ineligible for Medicare Part A and B (3,756) or fee-for-service (12,249) coverage. After excluding patients with Stage 0 (809) or Stage 4 (5,808) cancer, the final study sample consisted of 29,733 patients. Patients could have more than one reason for exclusion.

### Construction of Variables

Median income in each patient's ZIP code of residence was used as a proxy measure for socioeconomic status.[22] Proximal lesions were defined as those occurring at the splenic flexure or more proximally.[23] Chronic conditions were selected based on prior published indices as well as clinical judgment.[24] Using a modification of a previously specified algorithm, conditions were identified by searching inpatient, outpatient, and physician claims for each patient during the interval beginning 2 years before and concluding 60 days after cancer diagnosis.[24,25] This enabled the sensitivity of the claims-based approach t identifying comorbid conditions to be increased. Cancer-specific surgery, chemotherapy, and radiation therapy were identified according to International Classification of Diseases (ICD)-9 diagnostic and procedure codes that were derived from published sources.[17,26]

### Statistical Analysis

Cox proportional hazards models were used to examine the association between each patient characteristic and all-cause mortality during the follow-up period.[27] Data were censored at death or the end of calendar year 2002, whichever occurred first. Candidate covariates for the multivariable model included sociodemographic characteristics, cancer-specific characteristics (stage, histological grade, tumor location), and individual conditions. To address variability in use of care and health status, additional covariates were added, including the number of physician outpatient visits and the number of hospitalizations during the period between 24 and 2 months before cancer diagnosis.[28] To determine whether treatment differences mediated the relationship between specific chronic conditions and death, the analysis was repeated after adding cancer treatment–related variables to the model.

After the adjusted hazard ratios (HRs) were estimated for each condition, the PAR was calculated.[29,30] The PAR can be conceived of as a way of quantifying, at the population level, the proportion of deaths that might have been prevented if the specific condition were not present in any of the patients. Thus, these additional deaths are attributed to the specific condition. The PAR for each condition was derived using the formula

$$\mathrm{PAR} = \{Pe(\mathrm{HR} - 1)/(Pe(\mathrm{HR} - 1) + 1)\} \times 100$$

where $Pe$ = proportion of population that has the condition, and HR is the adjusted HR associated with the condition. Because some chronic conditions are related to one

another by factors such as common risk factors, there was a possibility that confounding could exist.[31] The analysis was therefore repeated using a derivation of Bruzzi's formula to assess the PAR of the three most common conditions.[29,30]

$$PAR = 1 - \sum_{j} \frac{\rho_j}{R_j}$$

In this formula, $\rho_j$, represents the proportion of death in stratum of conditions j, and $R_j$ is the adjusted HR from the Cox model. Cox models were assessed extensively by plotting log-negative-log survival function over log of time and Schoenfeld and other residuals over time to ensure the proportional hazards assumption was met. Ninety-five percent confidence intervals were generated by using the 2.5th and 97.5th percentiles derived from bootstrapping samples (1,000) using sampling with replacement on the complete cohort. The analyses were also repeated after replacing survival time in the Cox model with age at death and secondly after excluding patients who survived for less than 180 days. Because neither analysis yielded substantively different results, they are not reported herein.

Additional analyses were performed on the three conditions that had the highest PAR: congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetes mellitus. Two approaches were used to assess specific combinations of conditions. First, interaction terms were included for each pair of the three conditions (i.e., CHF by diabetes mellitus) to the model. Seven dummy variables were then created that reflected the different combinations of the three conditions (the reference is the group without any of the three conditions) and ran the Cox model using these variables together with all the covariates. The PAR for each of the seven combinations was calculated using the polytomous exposure level approach, which is similar to the formula for two-level exposure (above) but uses the sum of P*e* (HR – 1) of all exposure levels in the denominator.[31] The survival model was reestimated for each age group, and the PAR for the three conditions was calculated within each age group. Finally, to compare the effect of chronic conditions with that of advanced-stage cancer, predicted 5-year survival was estimated for patients grouped by chronic condition status and cancer stage. All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

## RESULTS

The mean age of the study cohort was 77.8 (range 67–99); 88% of the patients were white, and 55% were female. One fourth of the patients had rectal cancer, with the remainder diagnosed with cancers of the proximal (47.2%) or distal (26.3%) colon. Patients were evenly distributed according to stage, with 29.5% diagnosed at Stage 1, 38.0% at Stage 2, and 27.6% at Stage 3. The median follow-up was 4.1 years and ranged from 3 to 10 years. During the follow-up period, 54.8% of the patients died, with an overall death rate of 128.7 per 1,000 person-years.

CHF was diagnosed in 5,585 patients (18.8%); these patients were significantly more likely to die during the follow-up period than patients without CHF (76.9% vs 49.6%, $P < .001$) (Table 1). COPD was present in 20.9% of the study population, and 17.8% had a diagnosis of diabetes mellitus. Each of these conditions was significantly

**Table 1. Comorbid Conditions and Mortality in Older Patients with Colorectal Cancer**

| | | Died During Study Period | | | | |
|---|---|---|---|---|---|---|
| | | Patients with Condition | Patients without Condition | *P*-value* | | |
| Condition | Prevalence % | % | | | Adjusted HR (95% CI)† | PAR % (95% CI)‡ |
| Congestive heart failure | 18.8 | 76.9 | 49.6 | <.001 | 1.55 (1.49–1.62) | 9.42 (8.42–10.53) |
| Chronic obstructive pulmonary disease | 20.9 | 64.8 | 52.1 | <.001 | 1.29 (1.24–1.33) | 5.64 (4.67–6.59) |
| Diabetes mellitus | 17.8 | 62.0 | 53.2 | <.001 | 1.23 (1.18–1.28) | 3.92 (3.09–4.79) |
| Atrial fibrillation | 16.1 | 69.5 | 51.9 | <.001 | 1.22 (1.18–1.28) | 3.50 (2.72–4.32) |
| Cerebrovascular disease | 10.3 | 71.0 | 52.9 | <.001 | 1.25 (1.19–1.32) | 2.56 (1.85–3.24) |
| Dementia | 3.2 | 86.5 | 53.7 | <.001 | 1.68 (1.56–1.81) | 2.11 (1.63–2.62) |
| Chronic renal failure | 2.4 | 83.2 | 54.1 | <.001 | 1.77 (1.62–1.92) | 1.78 (1.38–2.24) |
| Peripheral vascular disease | 6.7 | 69.9 | 53.7 | <.001 | 1.22 (1.16–1.30) | 1.47 (1.01–1.95) |
| Liver disease | 1.4 | 69.0 | 54.6 | <.001 | 1.76 (1.56–1.98) | 1.03 (0.71–1.40) |
| Hip fracture | 6.0 | 65.0 | 54.1 | <.001 | 1.16 (1.09–1.24) | 0.96 (0.50–1.46) |
| Paralysis | 2.1 | 77.9 | 54.3 | <.001 | 1.27 (1.15–1.40) | 0.55 (0.25–0.91) |
| Rheumatological disorder | 2.4 | 57.1 | 54.7 | .16 | 1.13 (1.03–1.25) | 0.32 (0.07–0.62) |
| Venous thromboembolism | 3.0 | 63.2 | 54.5 | <.001 | 1.10 (1.01–1.20) | 0.31 (0.04–0.63) |
| Peptic ulcer disease | 7.8 | 65.8 | 53.8 | <.001 | NS | NA |

* *P*-value for proportion of death in patients with condition versus those without condition, derived from chi-square test.
† Adjusted for patient sociodemographic and cancer characteristics, as well as other comorbid conditions listed in Table 1. Referent category is patients without the conditions.
NS = hazard ratio (HR) not significantly different from 1.0 in the multivariate model; NA = not available, because population attributable risk (PAR) was not calculated when HR was not significant; CI = confidence interval from bootstrap results.

associated with mortality ($P < .001$ for both comparisons). Atrial fibrillation (16.1% of patients) and cerebrovascular disease (10.3%) were also among the more frequently diagnosed conditions. In bivariate analysis, all of these conditions were significantly associated with death, with the exception of rheumatological disorders (Table 2).

Although the HR associated with CHF was the fourth highest of the conditions studied (HR = 1.55, 95% confidence interval (CI) = 1.49–1.62), the PAR associated with CHF in the study cohort was the highest (9.3%, 95% CI = 8.4–10.5; Table 2). The PAR for COPD was 5.6% (95% CI = 4.7–6.6%), and for diabetes mellitus it was 3.9% (95% CI = 3.1–4.8%). Some conditions, such as liver disease, were associated with a higher HR than CHF but had a lower PAR because of lower disease prevalence. Kaplan-Meier survival curves for the three conditions with the highest PAR are shown in Figure 1; the difference in survival between patients with and without each of the conditions was apparent within the first year after diagnosis and was statistically significant in all three comparisons ($P < .001$).

There was a significant effect of primary surgical resection (HR = 0.73, 95% CI = 0.70–0.76) and chemotherapy (HR = 0.73, 95% CI = 0.79–0.87) on mortality risk, although adjusting for receipt of therapy had little effect on the hazards associated with any of the conditions. For instance, the adjusted HRs after accounting for treatment (1.54 for CHF, 1.23 for diabetes mellitus) were largely unchanged from the HRs derived from the original model (1.55 for CHF, 1.23 for diabetes mellitus).

Additional analyses focusing on the three conditions with the highest PAR (CHF, COPD, and diabetes mellitus) were performed. The PAR associated with heart failure tended to increase with increasing age (Table 3). The PAR was higher in patients aged 81 to 85 (PAR = 14.51%, 95% CI = 11.98–17.54%) and 86 and older (PAR = 11.08%, 95% CI = 8.26–14.21%; Table 3) than in the group aged 67 to 70, in which 6.3% (95% CI = 4.4–8.9%) of deaths were attributable to CHF. Conversely, the PAR associated with COPD and diabetes mellitus tended to decline with increasing age. The PAR associated with COPD was approximately 7% to 9% in the younger age groups, decreasing to 4% (81–85) and 2% ($\geq$86). Similarly, diabetes mellitus accounted for roughly 7% of deaths in the youngest age group but fewer than 2% in the oldest age group.

Combinations of chronic conditions occurred relatively frequently and accounted for a substantial amount of mortality (Table 3). Approximately 8.7% of patients had CHF without having concomitant COPD or diabetes mellitus. The PAR for CHF alone was 4.29% (95% CI = 3.68–4.94%), but more than half of the patients who had CHF also had one of the other conditions. For instance, CHF was diagnosed in patients who also had COPD (4.9% of the study sample) or diabetes mellitus (3.4%), whereas 1.8% had all three conditions. The PAR for CHF in combination with COPD was 3.9% (95% CI = 3.41–4.54%), indicating that nearly 4% of all deaths were attributable to the combination of these two conditions.

The hazard of death varied according to specific combinations of diabetes mellitus, CHF, and COPD. For instance, the adjusted HR for patients who were diagnosed with CHF and diabetes mellitus (2.12, 95% CI = 1.97–

**Table 2. Population Attributable Risk According to Age Group**

| | Heart Failure | | | Chronic Obstructive Pulmonary Disease | | | Diabetes Mellitus | | |
|---|---|---|---|---|---|---|---|---|---|
| Age | P (%) | HR (95% CI) | PAR (95% CI)* | P (%) | HR (95% CI) | PAR (95% CI)* | P (%) | HR (95% CI) | PAR (95% CI)* |
| Overall | 18.8 | 1.55 (1.49–1.62) | 9.45 (8.68–10.40) | 20.9 | 1.31 (1.26–1.37) | 5.34 (4.41–6.11) | 17.8 | 1.23 (1.18–1.28) | 3.59 (2.80–4.29) |
| 67–70 | 8.8 | 1.77 (1.52–2.05) | 6.31 (4.36–8.85) | 19.0 | 1.53 (1.37–1.71) | 9.12 (6.48–12.18) | 18.6 | 1.41 (1.25–1.58) | 7.02 (4.48–9.87) |
| 71–75 | 13.3 | 1.68 (1.52–1.86) | 8.31 (6.58–10.60) | 21.4 | 1.37 (1.26–1.48) | 7.28 (5.03–9.60) | 19.2 | 1.21 (1.11–1.32) | 3.89 (2.07–6.03) |
| 76–80 | 17.2 | 1.51 (1.39–1.65) | 8.10 (5.95–10.26) | 22.0 | 1.34 (1.24–1.44) | 6.92 (5.02–8.98) | 18.4 | 1.25 (1.15–1.35) | 4.40 (2.62–6.24) |
| 81–85 | 24.4 | 1.70 (1.57–1.84) | 14.51 (11.98–17.54) | 21.1 | 1.22 (1.12–1.32) | 4.36 (2.38–6.68) | 17.9 | 1.21 (1.11–1.31) | 3.54 (1.79–5.40) |
| $\geq$86 | 34.8 | 1.36 (1.26–1.47) | 11.08 (8.26–14.21) | 19.9 | 1.10 (1.01–1.20) | 1.89 (0.06–3.74) | 13.1 | 1.14 (1.03–1.26) | 1.78 (0.37–3.37) |

*Note:* Each row represents a unique model; the population attributable risk (PAR) estimates in the top row were derived from an adaptation of Bruzzi's formula.
*Confidence intervals (CIs) for PAR are from bootstrap results.
HR = adjusted hazard ratio derived from Cox proportional hazards model, adjusted for sociodemographic factors, cancer stage, grade, and other comorbid conditions listed in Table 1; P = prevalence of condition.

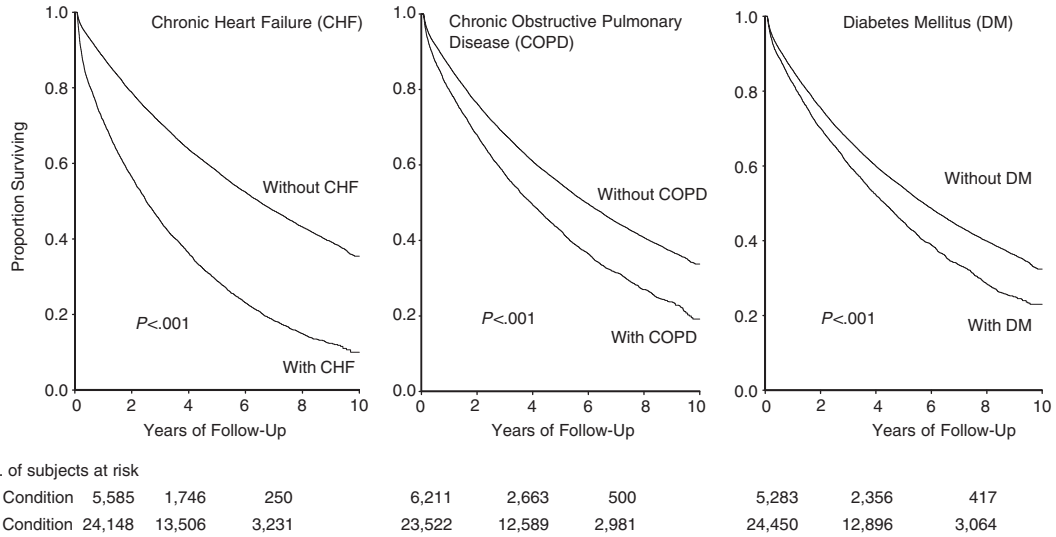


**Figure 1.** Survival after diagnosis of colorectal cancer according to chronic disease status.

2.29) was greater than the HRs associated with having CHF (1.62) or diabetes mellitus alone (1.31; *P* for interaction =0.84). To determine the effect of these combinations of conditions on mortality, interactions between the two specific conditions were tested for. For instance, in patients who had a diagnosis of CHF or diabetes mellitus in addition to COPD, the increase risk of death was less than the risk expected from their individual effects ($P < .01$ for each interaction). For instance, the HR for diabetes mellitus alone was 1.31 (95% CI = 1.24–1.38) and for COPD alone was 1.41 (95% CI = 1.35–1.48), whereas the HR for patients with COPD and diabetes mellitus was 1.43 (95% CI = 1.28–1.59). Hence, the addition of diabetes mellitus did not lead to substantial further increased risk of death in patients who had COPD.

Finally, predicted 5-year survival was estimated as a function of cancer stage and chronic condition status. In patients with no chronic conditions, the predicted 5-year survival was 78.3% (95% CI = 76.9–79.7%) for Stage 1, decreasing to about 68% for Stage 2 and 50% for Stage 3 patients (Table 4). In patients with Stage 1 colorectal cancer and only one chronic condition, the predicted survival ranged from about 71.4% for diabetes mellitus to 55.6% for CHF. Patients with two or more conditions had a predicted 5-year survival of 49.6%.

## DISCUSSION

There are several important implications of these findings. First, the effect of chronic conditions on colorectal cancer survival was found to be substantial. More than 9% of all deaths in this cohort of patients with Stage 1 through Stage 3 colorectal cancer were attributable to CHF, whereas 5% were attributable to COPD and almost 4% to diabetes mellitus. Furthermore, the effect of chronic conditions may be comparable with the effect of advanced-stage cancer. The predicted 5-year survival of a patient with Stage 1 cancer and no chronic conditions was found to be approximately 78%. If the same patient had multimorbidity or advanced stage cancer, the predicted survival decreased to approximately 50%. Because multimorbidity was so common, many older persons may die with, rather than from,

**Table 3. Multiple Concomitant Chronic Conditions and Risk of Death**

| Heart Failure | Chronic Obstructive Pulmonary Disease | Diabetes Mellitus | Prevalence n (%) | Died During Follow-Up % | HR* (95% CI) | PAR % (95% CI)† |
|---|---|---|---|---|---|---|
| – | – | – | 16,797 (56.5) | 46.6 | 1.00 | |
| + | – | – | 2,589 (8.7) | 74.8 | 1.62 (1.62–1.71) | 4.29 (3.68–4.94) |
| – | + | – | 3,616 (12.2) | 58.4 | 1.41 (1.35–1.48) | 4.02 (3.39–4.72) |
| – | – | + | 3,115 (10.5) | 54.3 | 1.31 (1.24–1.38) | 2.58 (2.03–3.22) |
| – | + | + | 620 (2.1) | 59.2 | 1.43 (1.28–1.59) | 0.70 (0.47–0.97) |
| + | – | + | 1,021 (3.4) | 79.3 | 2.12 (1.97–2.29) | 3.08 (2.60–3.61) |
| + | + | – | 1,448 (4.9) | 78.7 | 2.01 (1.88–2.15) | 3.93 (3.41–4.54) |
| + | + | + | 527 (1.8) | 77.6 | 2.08 (1.87–2.30) | 1.52 (1.18–1.89) |

* Adjusted hazard ratios (HRs) that account for other sociodemographic and clinic variable included in the full model; referent category is patients without any of the three comorbid conditions.
† Confidence intervals (CIs) for population attributable risk (PAR) are from bootstrap results.
+ = that the relevant International Classification of Diseases, Ninth Revision (ICD-9) code was noted in patient claims before their cancer diagnosis. – = absence of a claim consistent with a diagnosis.

**Table 4. Five-Year Survival According to Stage at Diagnosis and Chronic Condition Status**

| Number of Chronic Conditions | Predicted 5-Year Survival % (95% Confidence Interval) | | |
|---|---|---|---|
| | Stage 1 | Stage 2 | Stage 3 |
| 0 | 78.3 (76.9–79.7) | 67.4 (66.0–68.8) | 50.6 (48.9–52.5) |
| 1 | | | |
| Heart failure | 55.6 (49.7–62.2) | 51.7 (47.1–56.8) | 35.1 (29.7–41.6) |
| Diabetes mellitus | 71.4 (67.9–75.1) | 58.3 (54.8–62.1) | 43.0 (39.2–47.2) |
| Chronic obstructive pulmonary disease | 65.0 (61.6–68.6) | 55.7 (52.6–59.1) | 39.9 (35.8–43.7) |
| Any other condition* | 68.9 (66.4–71.4) | 62.0 (59.8–64.3) | 42.3 (39.6–45.2) |
| ≥2 | 49.6 (47.5–51.7) | 42.3 (40.6–44.1) | 27.7 (25.9–29.6) |

* Peripheral vascular disease, cerebrovascular diseases, dementia, paralysis, renal failure, liver disease, ulcers, rheumatological disease, hip fracture, atrial fibrillation, or venous thromboembolism.

their cancer. This underscores the importance of viewing cancer in the context of other chronic conditions and impairments. These findings also suggest that cancer death rates should be viewed with caution. Because attribution of cause of death at the individual patient level is challenging at best, a simple count of the number of older persons who died after a cancer diagnosis could substantially overestimate cancer mortality rates.

These data also add to prior work by demonstrating, in several ways, that a simple count of conditions is a suboptimal approach for evaluating chronic illness burden. First, the variation in PAR for the chronic conditions shows that some conditions will have a greater deleterious effect than others. A simple count of conditions would ignore these important distinctions. The relationship between PAR and age also varied; the PAR associated with CHF tended to increase with age, whereas the PAR for diabetes mellitus and COPD remained stable or declined with increasing age. Although the study was not designed to elucidate the etiology of these changes in PAR, it is likely that a survivor effect, as well as age-related changes in incidence and case ascertainment rates, contribute to these differences by age.[32–35] These findings further support the importance of identifying specific conditions, particularly when comparing outcomes across age groups.

Another finding that challenged the utility of the comorbidity count approach was the assessment of interactions between conditions. It was found that chronic conditions frequently occur in combination with one another and that specific combinations of conditions, such as CHF and diabetes mellitus or CHF and COPD, are deleterious at the population level. Although the combination of CHF and diabetes mellitus more than doubled the risk of death, the greater risks associated with CHF or diabetes mellitus alone were approximately 60% and 30%, respectively. However, not all combinations of conditions affected patients in a predictable manner. In patients with COPD, for instance, the increase in risk of death was approximately 40% regardless of whether they had diabetes mellitus in conjunction with their COPD. Hence, a simple "comorbidity count" can be misleading, because in some instances, diabetes mellitus would have little incremental effect on mortality (in patients who already had COPD), whereas in others, diabetes mellitus exerts a strong independent hazard of death (in patients without CHF or COPD).

The results also add to prior work by providing evidence that the mechanism through which multimorbidity affects cancer survivorship is independent of cancer therapy receipt. Adjusting for cancer treatment had little effect on the HR associated with any of the conditions investigated. This suggests that the noncancer conditions contribute to mortality more directly, independent of cancer or by decreasing functional reserves for confronting cancer.[36] This is consistent with recent analyses of patients with breast cancer that found that chronic disease burden was strongly associated with all-cause survival but not breast cancer–specific survival.[12,37]

There are several limitations to this analysis. Chronic conditions are not always reliably recorded in administrative claims. It is therefore likely that the analysis underestimated the prevalence and effect of conditions such as dementia and renal insufficiency.[38] Conversely, other conditions, such as COPD or CHF may be overdiagnosed as an etiology of shortness of breath in older persons. To increase the specificity, an algorithm was used for identifying conditions that requires two outpatient or one inpatient claims, as recommended previously.[24] In addition, SEER–Medicare data do not include other important measures of health status, such as functional disabilities or geriatric syndromes. Finally, although little difference was found in the PARs obtained for diabetes mellitus, COPD, and CHF using the Bruzzi-derived or the traditional PAR formula, investigations in other populations that involve clinically relevant interactions of conditions should also use both methods.[29,30]

The findings emphasize several important knowledge gaps. Because patients with comorbid conditions are frequently excluded from trials, subgroup analyses of these trials according to comorbidity status are not possible.[39] Because it was found that multimorbidity is common and clinically relevant, future work should explore the effect of multimorbidity on treatment effectiveness, as well as patient treatment preferences. Additional studies should investigate how multimorbidity affects nonfatal health outcomes such as hospitalizations, healthcare utilization, skilled nursing facility placement, and functional decline.[40,41] Finally, including patients with and without cancer in study samples will enable investigators to understand the independent effects of cancer and noncancer conditions and how their concurrence affects patients. To improve care

of older persons with cancer, we need to further our understanding of how chronic conditions affect health outcomes.

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