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ORIGINAL REPORT

Determinants of Early Mortality Among 37,568 Patients With Colon Cancer Who Participated in 25 Clinical Trials From the Adjuvant Colon Cancer Endpoints Database

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ABSTRACT

Purpose

Factors associated with early mortality after surgery and treatment with adjuvant chemotherapy in colon cancer are poorly understood. We aimed to characterize the determinants of early mortality in a large cohort of colon cancer trial participants.

Methods

A pooled analysis of 37,568 patients in 25 randomized trials of adjuvant systemic therapy was conducted. Multivariable logistic regression models with several definitions of early mortality (30, 60, and 90 days, and 6 months) were constructed, adjusting for clinically and statistically significant variables. A nomogram for 6-month mortality was developed and validated.

Results

Median age among patients was 61 years, patient demographics included 54% men and 90% White, 29% and 71% had stage II and III disease, respectively, and 79%, 20%, and 1% had an Eastern Cooperative Oncology Group performance status (PS) of 0, 1, and ≥ 2, respectively. Early mortality was low: 0.3% at 30 days, 0.6% at 60 days, 0.8% at 90 days, and 1.4% at 6 months. Of those patients who died by 6 months post–random assignment, 40% had documented disease recurrence prior to death. Early disease recurrence was associated with a markedly increased risk of death during the first 6 months post-treatment (hazard ratio, 82.6; 95% CI, 66.9 to 102.1). In prognostic analyses, advanced age, male sex, poorer PS, increasing ratio of positive to examined lymph nodes, earlier decade of enrollment, and higher tumor stage and grade predicted a greater likelihood of early mortality, whereas treatment received was not strongly predictive. A multivariable model for 6-month mortality showed strong optimism-adjusted discrimination (concordance index, 0.73) and calibration.

Conclusion

Early mortality was infrequent but more prevalent in patients with advanced age and a PS of ≥ 2, underscoring the need to carefully consider the risk-to-benefit ratio when making treatment decisions in these subgroups.

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INTRODUCTION

Randomized controlled trials in oncology are the gold standard for developing novel cancer therapeutics, determining their optimal delivery, and evaluating their efficacy. Currently, over 11,000 clinical trials listed by the National Cancer Institute are accepting participants; however, only 2% to 4% of patients with cancer elect to participate in clinical studies.[1-3] Low enrollment rates slow the progress of trials and may result in delayed study completion or even study closure.[4,5] Likewise, recruitment of patients who are at substantial risk of significant treatment toxicity or early mortality compromises trial integrity, poses greater harm than benefit to participants, and complicates interpretation of trial results.[1-3] Thus, the selection of appropriate participants for clinical trials is important, but the process can be challenging.

Recognizing the value of enriching patient selection for phase I trial entry, Olmos et al[6]

collected data from 2,182 patients who were treated in phase I trials across 14 European institutions. The authors derived eight independent prognostic factors for 90-day mortality with the intention of improving future phase I trial eligibility criteria.[6] Additional research groups have devised similar systems, such as the Royal Marsden Hospital score,[7,8] to better identify patients for whom prognosis is sufficiently poor and for whom the harms of trial participation outweigh any potential benefits.

Prior analyses exploring this issue were focused on phase I trials or were hindered by interpractice heterogeneity as well as limited sample sizes.[9-11] The majority of present-day clinical trials of early-stage and metastatic cancers generally restrict enrollment to patients with an expected life expectancy of at least 3 to 6 months[12]; however, this criterion can be vague and largely dependent on physician clinical judgement. In many cancers for which disease trajectory and overall survival can be highly variable, an ability to objectively and reliably predict early death could inform both patient selection and future trial design. By using the large Adjuvant Colon Cancer Endpoints (ACCENT) database, our primary aims were to define prognostic factors and to develop a nomogram that can be used to guide risk-to-benefit assessments among patients being considered for phase III adjuvant colon cancer clinical trials.

METHODS

Description of the Database

The ACCENT database contains patient-level information on more than 35,000 patients participating in 25 adjuvant phase III studies since 1977 (Appendix Table A1, online only).[13-15] Across these trials, median length of follow-up among surviving patients is 7.5 years. In this analysis, the primary outcome was early mortality, defined as death resulting from any cause by 30 days, 60 days, 90 days, and 6 months post–random assignment. At the 6-month time point, recurrences were also examined to distinguish deaths as a result of recurrent disease from deaths resulting from other causes, such as potential treatment complications.

Statistical Methods

Descriptive statistics for patient characteristics and mortality rates at each time point were summarized. Death rates were described by treatment across all time points and by recurrence status among those patients who died by 6 months. The impact of preceding disease recurrence on the likelihood of 6-month survival was examined by including recurrence as a time-dependent covariate in a Cox proportional hazards regression model that was right-censored at 6 months and adjusted for other patient characteristics.

Baseline patient factors that were evaluated for prognostic associations with early mortality included age, sex, race (white, black, Asian, other), performance status (PS; 0, 1, $\geq$ 2), disease stage (II and III), body mass index, tumor stage (T1 to T4), tumor grade (1, 2, $\geq$ 3), lymph node ratio (LNR; ratio of positive lymph nodes to nodes examined), primary tumor location (single left, single right, single transverse/flexures, any multiple), decade randomly assigned (1970s, 1980s, 1990s, 2000s), and treatment (surgery alone, fluorouracil plus leucovorin [5-FU + LV] variations, 5-FU + LV plus oxaliplatin, 5-FU + LV plus irinotecan). Missing baseline data were imputed via multiple imputation; specifically, bootstrapped regression with predictive mean matching was used to maintain a level of variability in the imputed data similar to that which exists in the available data.[16]

Univariable regression models were fitted to identify significant predictors of early mortality at each time point, for which significance required both $P < 0.05$ and clinically meaningful effects (odds ratios [OR]). In these models, continuous variables were modeled with restricted

cubic splines[16] and tested for possible nonlinearity of the effects on the log-odds scale. Where significant nonlinearity was found, effects were plotted on the probability scale with 95% confidence bands for visual inspection of the shape of effect, and spline modeling was subsequently used in multivariable models; otherwise, standard linear modeling was used. Two-way interactions between significant univariable contributors were also tested, for which both $P < 0.01$ for the interaction effect and clinically differentiable effects across factor levels indicated significance. Multivariable models were constructed from statistically and clinically significant variables and interaction effects for each time point. Variables that no longer contributed statistically or clinically meaningful effects in multivariable models were excluded. Disease recurrence was also excluded from consideration in these prognostic models, as recurrence status is unknown at the time adjuvant treatment decisions are made.

A nomogram was constructed from the final multivariable model for mortality by 6 months. As measures of internal calibration, the concordance index, which is equivalent to the area under the receiver-operator characteristic curve, and a nonparametric smoothed calibration plot of actual versus predicted outcomes were reported.[17] External validation of the nomogram was performed using data from 3,227 patients enrolled in the clinical trial N0147,[18] for which average nomogram-predicted and actual early mortality rates were examined, both overall and within patient subgroups. In both univariable and multivariable models, statistically significant categorical effects, standard errors, and ORs were computed. All analyses were performed using R software (The R Project for Statistical Computing; The R Foundation, Vienna, Austria).[5]

RESULTS

Descriptive Statistics

A total of 37,568 patients from 25 ACCENT trials were analyzed. Baseline patient demographics and disease characteristics are summarized in Table 1. Early mortality rates were 0.3% at 30 days, 0.6% at 60 days, 0.8% at 90 days, and 1.4% at 6 months. The proportions of patients alive and dead at each time point are presented by treatment in Table 2. Patients treated with surgery alone exhibited the highest early mortality rates over time, from 0.6% at 30 days to 2.0% by 6 months. Adjuvant chemotherapy with 5-FU + LV alone or 5-FU + LV plus irinotecan were associated with mortality rates from 0.3% and 0.4% at 30 days to 1.5% and 1.3% by 6 months, respectively. The lowest early mortality rates across time points occurred among patients treated with 5-FU + LV plus oxaliplatin and ranged from 0.2% at 30 days to 1.2% at 6 months.

Impact of Recurrence on Mortality

Among patients who died by 6 months post–random assignment, 40.1% had documented disease recurrence prior to death, 50.2% died without recurrence, and 9.3% had insufficient information to analyze recurrence status at the time of death. These rates differed according to stage of disease. Among patients with stage II disease who died by 6 months, 22.3% had disease recurrence prior to death, 74.1% died without disease, and 3.6% had insufficient recurrence information at the time of death. In contrast, among patients with stage III disease who died by 6 months, 44.6% had disease recurrence prior to death, 43.9% did not have recurrence, and 11.4% had inadequate information on recurrence. Of note, early recurrence was associated with an 82-fold increased risk of death during the first 6 months post-treatment in a Cox proportional hazards regression model that was adjusted for patient age, PS, grade, LNR, and decade of

Table 1. Demographics and Disease Characteristics of Patients Used for the Early Mortality Analyses

Variable	Value
Age, years	
Mean (SD)	50 (11)
Median (IQR)	61 (53-68)
Sex, No. (%)	
Male	20,389 (54)
Female	17,179 (46)
Race, No. (%)	
White	28,679 (90)
Black	1,785 (6)
Asian	601 (2)
Other	633 (2)
Missing	5,870 (16)
Performance status, No. (%)	
0	25,108 (79)
1	6,275 (20)
$\geq$ 2	300 (1)
Missing	5,179 (14)
Body mass index	
Mean (SD)	26 (5)
Median (IQR)	26 (23-29)
Missing, No. (%)	7,786 (21)
Stage, No. (%)	
II	10,780 (29)
III	26,788 (71)
Tumor stage	
T1	803 (2)
T2	3,518 (11)
T3	24,603 (76)
T4	3,465 (11)
Missing	5,179 (14)
Tumor grade	
1	2,915 (14)
2	14,339 (67)
$\geq$ 3	4,048 (19)
Missing	16,266 (43)
Node ratio	
Mean (SD)	0.21 (0.26)
Median (IQR)	0.12 (0.00-0.33)
Missing, No. (%)	9,420 (25)
Decade enrolled, No. (%)	
1970s-1980s	5,669 (15)
1990s	17,940 (48)
2000s	13,955 (37)
Missing	4 (0)
Treatment, No. (%)	
Surgery	2,362 (6)
5-FU + LV	27,121 (72)
5-FU + LV plus irinotecan	2,203 (6)
5-FU + LV plus oxaliplatin	5,882 (16)
Death by 30 days, No. (%)	
Yes	109 (0.3)
No	37,356 (99.7)
Missing	103 (0.3)
Death by 60 days, No. (%)	
Yes	215 (0.6)
No	37,223 (99.4)
Missing	130 (0.3)
Death by 90 days, No. (%)	
Yes	281 (0.8)
No	37,133 (99.2)
Missing	154 (0.4)
Death by 6 months, No. (%)	
Yes	540 (1.4)
No	36,825 (98.6)
Missing	203 (0.5)
(continued in next column)	

Table 1. Demographics and Disease Characteristics of Patients Used for the Early Mortality Analyses (continued)

Variable	Value
Recurrence by 30 days, No. (%)	
Yes	113 (0.3)
No	37,086 (99.7)
Missing	369 (1.0)
Recurrence by 60 days, No. (%)	
Yes	226 (0.6)
No	36,877 (99.4)
Missing	465 (1.2)
Recurrence by 90 days, No. (%)	
Yes	384 (1.0)
No	36,651 (99.0)
Missing	533 (1.4)
Recurrence by 6 months, No. (%)	
Yes	1,232 (3.3)
No	35,637 (96.7)
Missing	699 (1.9)

Abbreviations: 5-FU + LV, fluorouracil plus leucovorin; IQR, interquartile range; SD, standard deviation.

enrollment (hazard ratio, 82.6; 95% CI, 66.9 to 102.1). A series of two-variable models containing both recurrence and a patient or disease characteristic (eg, recurrence and age) showed statistically unchanged ORs and significance levels for patient factors after adjustment, indicating the relative independence and collective importance of these contributors to patients' early mortality.

Univariable Analyses

Age was correlated with early mortality at every time point ($P < .001$), and this association was found to increase with age in a nonlinear fashion (Fig 1A). Another strong predictor of early mortality was PS, where worse PS was highly associated with early mortality at all time points ($P < .001$ for 30, 60, and 90 days, and 6 months; 6 month PS 1 v PS 0 OR, 1.57; PS $\geq$ 2 v PS 0 OR, 3.65). Tumor grade was similarly associated, with higher risk of early mortality for higher-grade tumors (30 days $P = .002$; 60 days $P < .001$; 90 days $P < .001$; 6 months $P < .001$; grade 2 v 1 OR, 1.39; grade $\geq$ 3 v 1 OR, 3.52). T stage was also correlated with early mortality, although this relationship was not uniform over time and the risk did not increase monotonically (30 days $P = .01$; 60 days $P = .009$; 90 days $P = .06$; 6 months $P < .001$; T2 v T1 OR, 2.06; T3 v T1 OR, 1.85; T4 and T1 OR, 2.88). Early mortality was also greater in patients with stage III than stage II disease at 60 days ($P = .008$; OR, 1.57) and remained higher at 90 days ($P = .014$; OR, 1.43) and at 6 months ($P < .001$; OR, 1.55). A higher LNR was correlated with higher early mortality at 60 days ($P < .001$), 90 days ($P < .001$), and 6 months ($P < .001$), and this effect was nonlinear on the log-odds scale (Fig 1B). Decade of enrollment was not a significant predictor of early mortality until 6 months ($P = .001$; 1990s v 1970s to 1980s OR, 0.93; 2000s v 1970s to 1980s OR, 0.67). Male sex was associated with increased mortality at 30 days ($P = .038$; OR, 1.51), but it was not significantly associated at later time points. Early mortality rates were not associated with treatment, race, body mass index, or the number or location of primary tumors.

Table 2. Number of Deaths and Survivors and Death Rate at Each Time Point by Treatment

Variable	30 Days	60 Days	90 Days	6 Months
No. of deaths				
Overall	109	215	281	540
Surgery	13	20	23	46
5-FU + LV	76	149	200	393
5-FU + LV plus irinotecan	9	16	17	29
5-FU + LV plus oxaliplatin	11	30	41	72
No. of survivors				
Overall	37,356	37,223	37,133	36,825
Surgery	2,347	2,340	2,336	2,313
5-FU + LV	26,973	26,887	26,826	26,611
5-FU + LV plus irinotecan	2,193	2,182	2,181	2,169
5-FU + LV plus oxaliplatin	5,843	5,814	5,790	5,732
Death rate, %				
Overall	0.29	0.57	0.75	1.4
Surgery	0.55	0.85	0.98	2.0
5-FU + LV	0.28	0.55	0.74	1.5
5-FU + LV plus irinotecan	0.41	0.73	0.77	1.3
5-FU + LV plus oxaliplatin	0.19	0.51	0.70	1.2

Abbreviation: 5-FU + LV, fluorouracil plus leucovorin.

Interaction Analyses

Among all possible two-way variable interactions at each time point, the only statistically significant and clinically meaningful interaction that occurred was between age and tumor grade at 6 months. Specifically, the risk of early mortality increased with both age and grade, with worse tumor grade having a stronger impact on early mortality with advanced age ($P = .001$).

Multivariable Analyses

The patient characteristics found to contribute both statistically and clinically to early mortality in univariable models, in addition to those deemed to be of sufficient clinical interest despite lack of statistical significance (decade of random assignment and treatment), were carried forward and evaluated in multivariable models for each time point. A two-way interaction between age and grade was further considered at 6 months. Final models retaining statistically and clinically relevant terms are shown in Table 3.

In the final model for early mortality at 30 days, only age ($P < .001$), PS ($P < .001$), and tumor grade ($P = .009$) remained after removal of nonsignificant terms, with increased risk for advanced age, worse PS, and higher grade. The final models at 60 and 90 days also included age (both $P < .001$), PS (both $P < .001$), and grade (60 days $P = .004$; 90 days $P < .001$), but further included LNR (60 days $P = .010$; 90 days $P < .001$), where increased LNR corresponded to greater risk of early mortality. The final model for early mortality at 6 months included age ($P < .001$), PS ($P = .002$), tumor grade ($P < .001$), LNR ($P < .001$), T stage ($P = .005$), and decade of enrollment ($P = .005$), where increased T stage and earlier decade of enrollment were associated with higher risk of death. Of note, the two-way interaction between age and tumor grade considered at 6 months was not included in the final model, and treatment group was nonsignificant after adjustment and not significant at any time points.

Nomogram for 6-Month Mortality: Internal Validation

The final multivariable model for mortality at 6 months showed strong internal validity, with a discrimination concordance index of 0.732 indicating a 73.2% correct ordering of risk across pairs of patients, and good calibration of observed versus predicted outcomes as shown in Figure 2. A nomogram representation of the model is provided in Figure 3, where, for a specific patient, the predicted probability of 6-month mortality can be computed (Appendix, online only).
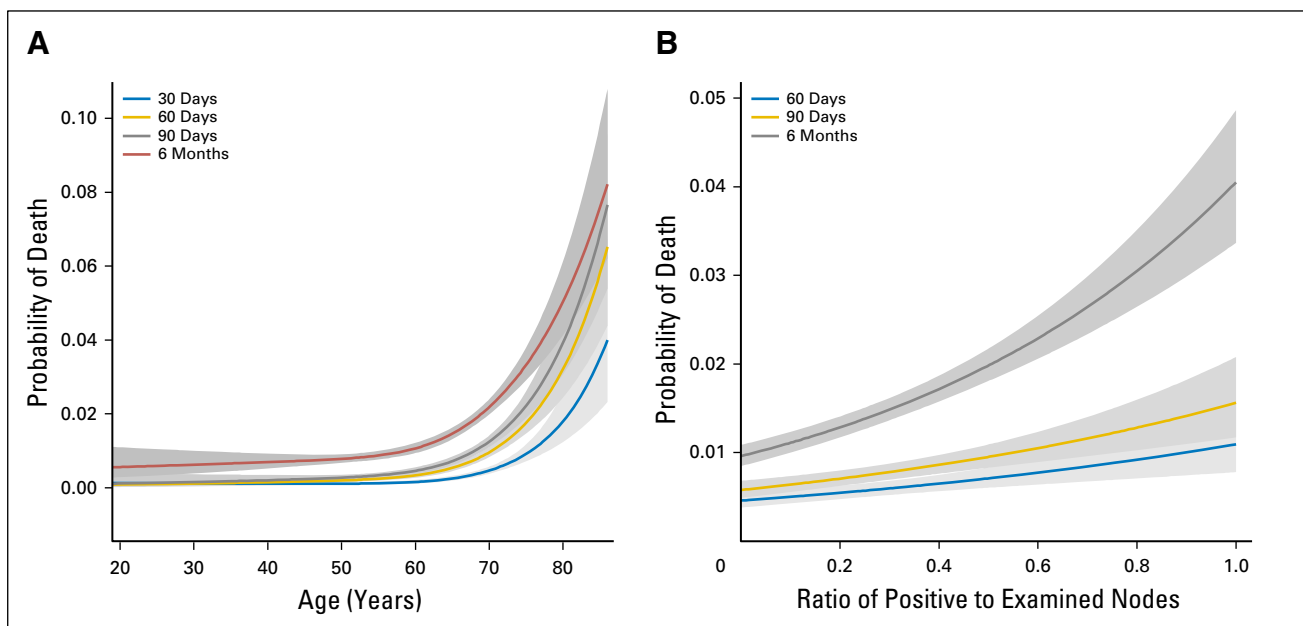
Fig 1. Continuous effects of (A) age at 30, 60, and 90 days, and 6 months; (B) lymph node ratio at 60 and 90 days and 6 months. Shaded gray regions are 95% CIs.
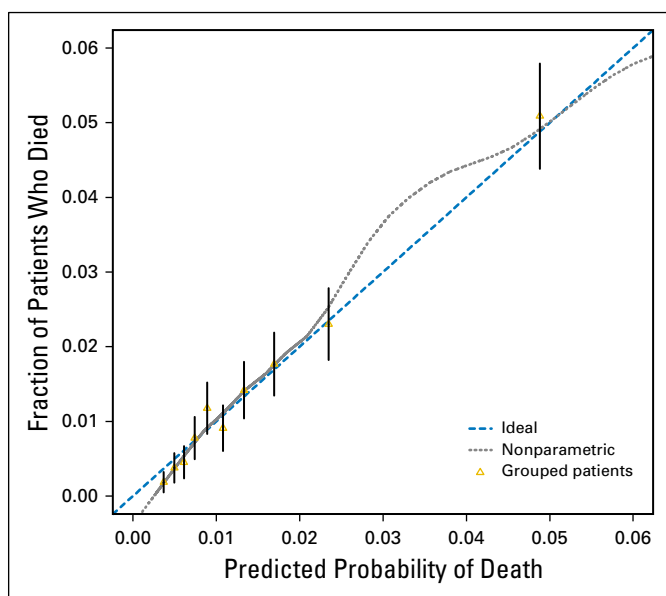
Table 3. Empirical Probabilities of Early Mortality and Multivariable Model-Based (Adjusted) Factor ORs, 95% CIs, and *P* Values for Early Mortality at Each Time Point

Variable	30 Days			60 Days			90 Days			6 Months		
	Rate	OR (95% CI)	*P*	Rate	OR (95% CI)	*P*	Rate	OR (95% CI)	*P*	Rate	OR (95% CI)	*P*
Age, years			< .001			< .001			< .001			< .001
40	0.0011	0.71 (0.33 to 1.49)		0.0006	0.43 (0.22 to 0.83)		0.0009	0.43 (0.25 to 0.76)		0.0042	0.65 (0.47 to 0.90)	
50	0.0011	0.72 (0.47 to 1.10)		0.0016	0.59 (0.42 to 0.83)		0.0022	0.60 (0.45 to 0.79)		0.0074	0.74 (0.60 to 0.91)	
60	0.0015	—		0.0040	—		0.0054	—		0.0128	—	
70	0.0046	2.58 (1.88 to 3.54)		0.0099	2.52 (2.01 to 3.15)		0.0128	2.46 (2.02 to 2.98)		0.0218	1.87 (1.57 to 2.24)	
80	0.0178	8.61 (5.34 to 13.9)		0.0251	7.58 (5.35 to 10.7)		0.0309	7.17 (5.27 to 9.75)		0.0374	4.05 (3.11 to 5.28)	
PS			< .001			< .001			< .001			.0015
0	0.0020	—		0.0044	—		0.0061	—		0.0127	—	
1	0.0058	2.33 (1.56 to 3.47)		0.0098	1.78 (1.33 to 2.38)		0.0114	1.47 (1.13 to 1.91)		0.0198	1.30 (1.07 to 1.58)	
≥ 2	0.0158	4.32 (1.82 to 10.3)		0.0316	4.11 (2.22 to 7.61)		0.0342	3.18 (1.77 to 5.72)		0.0449	2.07 (1.24 to 3.47)	
Grade			.0086			.0041			< .001			< .001
1	0.0021	—		0.0044	—		0.0050	—		0.0084	—	
2	0.0025	1.14 (0.60 to 2.16)		0.0051	1.07 (0.69 to 1.68)		0.0066	1.23 (0.81 to 1.87)		0.0116	1.32 (0.96 to 1.82)	
≥ 3	0.0050	2.10 (1.06 to 4.15)		0.0092	1.75 (1.08 to 2.84)		0.0127	2.14 (1.38 to 3.34)		0.0289	2.85 (2.04 to 3.97)	
LNR						.0099			< .001			< .001
0.00				0.0046	1.22 (1.05 to 1.42)		0.0058	1.27 (1.12 to 1.45)		0.0096	1.50 (1.37 to 1.64)	
0.50				0.0071			0.0095			0.0198		
1.00				0.0109			0.0156			0.0405		
T stage												.0051
T1										0.0074	—	
T2										0.0251	1.87 (0.85 to 4.11)	
T3										0.0136	2.11 (0.99 to 4.49)	
T4										0.0211	2.93 (1.34 to 6.38)	
Decade												.0050
< 1990s										0.0171	—	
1990s										0.0159	0.85 (0.67 to 1.08)	
2000s										0.0115	0.66 (0.51 to 0.86)	

NOTE. LNR is modeled as linear. Age is modeled as continuous and nonlinear, but spline-derived ORs versus age 60 are shown for selected ages along the continuum.
Abbreviations: —, reference group; < 1990s, enrolled prior to January 1, 1990; LNR, lymph node ratio; OR, odds ratio; PS, performance status.

Fig 2. Calibration of the final model for 6-month mortality.

Nomogram for 6-Month Mortality: External Validation With N0147 Patients

Across the 3,227 patients from trial N0147 with fully available nomogram and outcome data, 36 patients (1.1%) died by 6 months, exactly matching the average nomogram-predicted probability of 1.1% for 6-month mortality across patients. Within all subgroups of N0147 patients differentiated by the variables contained in the nomogram, average nomogram-predicted rates of early mortality fell within the 95% CIs for actual early mortality rates, with one exception: among patients with T4 tumors, the average nomogram-predicted early mortality rate was 0.37% higher than the upper 95% CI of the actual rate (Appendix Table A2, online only).

The ability of this model to distinguish between low-risk and high-risk patients can be demonstrated by considering two hypothetical individuals who might be encountered in practice: Patient A is 50 years old with a PS of 0 and an LNR of 0, whereas Patient B is 75 years old with a PS of 1 and an LNR of 0.40. We further assume that both patients have T3 tumors for which they recently received treatment. Our model predicted that Patient A has a 0.37% chance of early death by 6 months (95% CI, 0.30% to 0.47%) whereas Patient B has a 2.9% chance of early death (95% CI, 2.3% to 3.7%); that is, the risk of early mortality for Patient B is predicted to be 7.7 times greater than the risk for Patient A.

DISCUSSION

In this pooled analysis of patient-level data from individuals with colon cancer enrolled in phase III trials of adjuvant systemic therapy, early mortality at various time points within the first 6 months of random assignment were low, ranging from 1.2% to 2.0%, depending on the treatment received. In the subgroup of patients that experienced early death by 6 months, a significant proportion occurred in individuals in whom there was a documented early recurrence. This finding persisted when recurrence was examined as

a time-varying factor in the multivariable model for early mortality. For the under-represented subset of study participants that was either elderly or had a poor PS, risk of early death was particularly high. In an effort to facilitate early prognostication, a nomogram was developed and validated both internally and externally.

Our observation that mortality rates were low highlights the fact that current inclusion and exclusion criteria of clinical trials are effective in identifying eligible patients who may potentially benefit from study participation without experiencing excessive risk of serious harm. This can inform the treatment decision-making process, and may be particularly valuable for clinicians who are screening potential study participants and providing reassurance to patients and families who are considering study enrollment. Because trials are costly and resource intensive, this approach to patient selection further optimizes internal validity by minimizing unexpected attrition of patients as a result of toxicities or death that could otherwise compromise trial integrity, prompt slow accrual or study closure, or complicate the subsequent interpretation of results.

Of interest, mortality rates were lowest in the subset of patients that received adjuvant therapy, especially FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin; 1.2%), and highest in the group that underwent surgery alone without further postoperative therapy (2.0%). Contrary to the general assumption that systemic therapy exerts its effect mainly by reducing late recurrences, this observation suggests that chemotherapy may also prevent early recurrences, even within the first six months of treatment. Our current finding that nearly one half of the observed early deaths were preceded by a documented recurrence supports this hypothesis. Sargent et al[19] previously showed that adjuvant therapy significantly reduces the risk of early recurrences. Our observations further underscore the safety and tolerability of modern adjuvant chemotherapy, such as FOLFOX, as evidenced by the fact that the short-term risk of death with adjuvant treatment is lower than with surgery alone or 5-FU therapy alone in this study.

Consistent with prior research, patients with colon cancer who are of advanced age or who have poor PS were under-represented in most contemporary trials of adjuvant systemic therapy that were included in this pooled analysis.[20,21] Those patients who enrolled were more likely to experience early mortality, which demonstrated that many of these studies were not designed to accommodate the vulnerabilities of these demographic subgroups. In recent years, clinical trials specific to the elderly and to those with poor functional status have emerged, albeit infrequently. Studies such as AVEX and FOCUS2 limited enrollment to patients with metastatic colorectal cancer who were age 70 years and older and who had an ECOG PS of $\geq$ 2, respectively, and confirmed that it was feasible and effective to tailor studies to the needs of these under-represented patient populations.[22-25] Both of these clinical trials were performed among metastatic patients, so similar efforts are needed in the adjuvant colon cancer setting.

One of the distinguishing features of this study is the development of an easy-to-use, well-calibrated, and internally and externally valid nomogram that allows for the prediction of mortality at 6 months after study randomization. On the basis of results from the multivariable model, this nomogram incorporates parameters that are readily available at baseline. Such a tool can be valuable because patients considering enrollment in clinical trials must frequently consider many factors, including the likelihood of
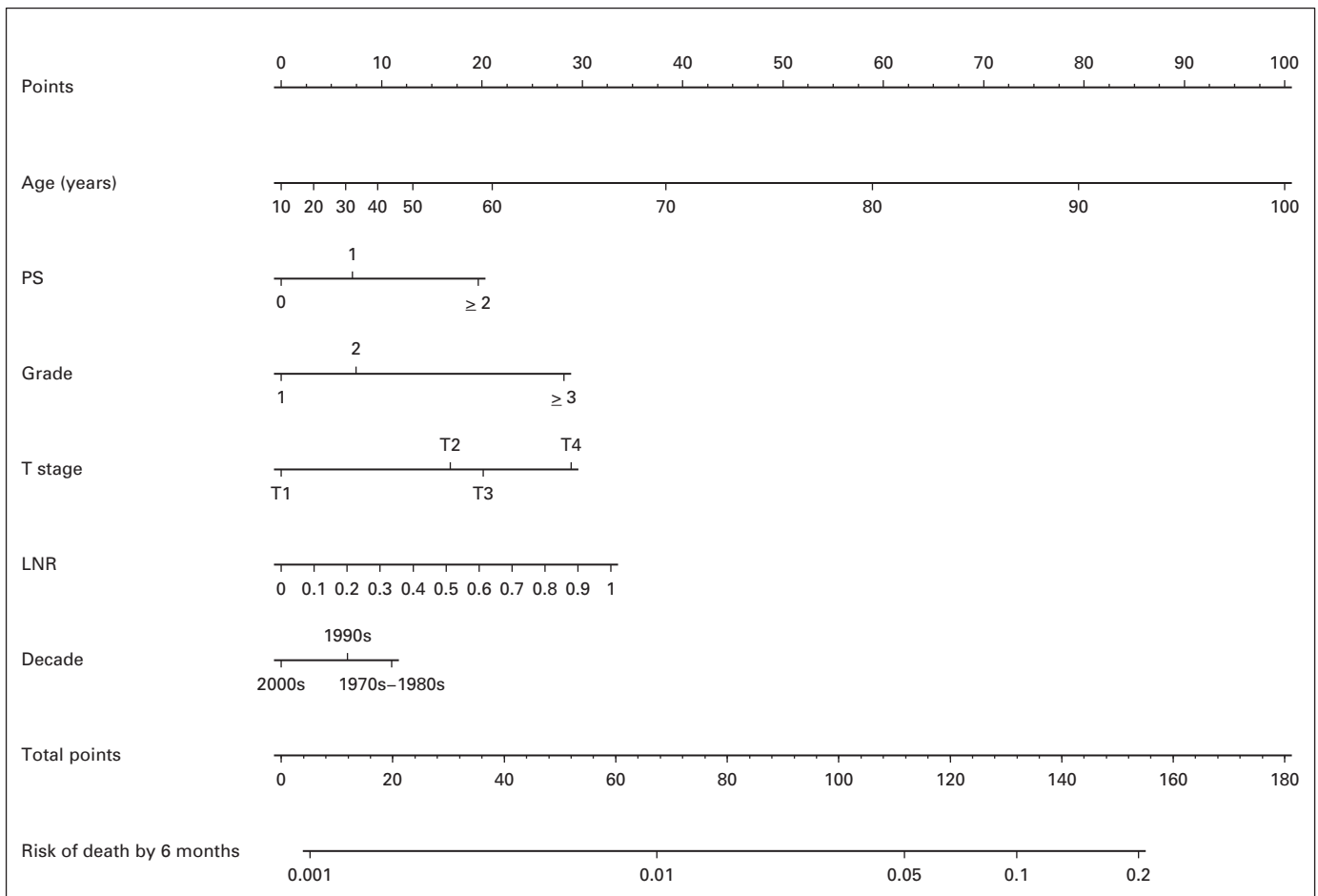
Fig 3. Nomogram for 6-month mortality. LNR, lymph node ratio; PS, performance status.

the treatment being effective, the time and cost involved, the potential for other alternatives, and the risk of toxicities or death. A quantitative assessment of the risk of death related to study treatments can be exceedingly difficult, especially when therapies tested in phase III trials are still considered experimental and highly variable. Therefore, clinicians often have little data on which to base their risk-to-benefit discussions with potential clinical trial patients. Although careful and diligent follow-up of study participants is already an established component of most clinical trial protocols, our nomogram can further augment care by identifying individuals for whom increased vigilance may be necessary.

Our findings should be interpreted in the context of several limitations. First, although we were able to classify deaths into those patients with documented cancer recurrences versus those without, we were unable to specifically determine the proportion of deaths attributable to treatment-related toxicities. Second, our findings are applicable only to patients with colon cancer who were enrolled in clinical trials of adjuvant systemic therapy, and the generalizability to other cancers, metastatic disease, and nontrial populations are unclear. However, these limitations should be weighed against the strengths of the study, which include the large cohort size, the inclusion of many clinical trials across different decades, and development of a validated nomogram that could prove useful in future clinical trials.

In summary, early mortality rates were low among patients with colon cancer who participated in adjuvant systemic therapy clinical trials. However, elderly patients and those with poor PS experienced worse early prognosis, lending importance to the emerging number of clinical trials that are specifically designed to represent these subpopulations. A nomogram on the basis of individual patient characteristics may be a potentially useful tool that can quantify the risk of early death and, thus, better inform discussions between clinicians and prospective trial participants as well as facilitate the informed consent process.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Determinants of Early Mortality Among 37,568 Patients With Colon Cancer Who Participated in 25 Clinical Trials From the Adjuvant Colon Cancer Endpoints Database

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Appendix

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Instructions for Use of the Nomogram for 6-Month Mortality

Risk points associated with each variable are first obtained via vertical translation of the variable value of the patient (eg, tumor stage at T3) to the scale labeled Points in the nomogram, that is, a T3 tumor contributes 20 points to the 6-month mortality risk. Next, the points associated with each variable value for the patient are totaled across the variables. This total is then located on the scale Total Points and vertically mapped to obtain the prediction of interest (eg, 112 total points corresponds to a 6-month mortality rate of approximately 5%).

Table A1. ACCENT Trials Used for Early Mortality Analyses

Trial	Years	Treatment Arm	No. of Participants
NSABP C01	1977-1983	Surgery alone *v* MOF	724
NSABP C02	1984-1988	Surgery alone *v* PVI + 5-FU	686
NSABP C03	1987-1989	MOF *v* FU + LV	1,042
NSABP C04	1989-1990	5-FU + LEV *v* 5-FU + LV *v* 5-FU + LV + LEV	2,083
NSABP C05	1991-1994	5-FU + LV *v* 5-FU + LV + IFN	2,136
NSABP C06	1997-1999	IFU + LV *v* UFT + LV	1,556
NSABP C07	2000-2002	5-FU + LV *v* FOLFOX	2,434
NSABP C08	2004-2006	mFOLFOX6 ± Bev	2,612
CALGB 89803	1999-2001	5-FU + LV *v* 5-FU + LV + IFL	1,239
FFCD	1982-1990	Surgery alone *v* 5-FU + LV	256
GERCOR	1996-1999	Bolus *v* infusional 5-FU + LV	900
GIVIO	1989-1992	Surgery alone *v* 5-FU + LV	846
INT-0035	1984-1987	Surgery alone *v* 5-FU + LEV	926
INT-0089	1990-1992	5-FU + LEV *v* 5-FU + LV (HD or LD) *v* 5-FU + LV + LEV	3,363
MOSAIC	1998-2001	5-FU + LV *v* FOLFOX	2,241
NCCTG-78-48-52	1978-1984	Surgery alone *v* 5-FU + LEV	247
NCCTG-87-46-51	1988-1989	Surgery alone *v* 5-FU + LV	408
NCCTG-89-46-51	1989-1991	5-FU + LV ± LEV for 6 or 12 months	914
NCCTG-91-46-53	1993-1998	5-FU + LV + HD or standard LEV	878
NCIC	1987-1992	Surgery alone *v* 5-FU + LV	359
PETACC-3	1999-2002	5-FU + LV (AIO or LVFU2) *v* ± IFL	3,186
QUASAR	1994-1997	5-FU + LV (HD or LD) ± LEV	3,507
SWOG 9415	1995-1999	Bolus *v* infusional 5-FU + LEV + LV	939
SIENA	1984-1990	Surgery alone *v* 5-FU + LV	239
XACT	1998-2001	5-FU + LV *v* Cap	1,983
XELOXA	2003-2004	5-FU + LV *v* XELOX	1,864
Complete ACCENT database	1977-2004		37,568

Abbreviations: 5-FU, fluorouracil; AIO, folic acid, fluorouracil, and irinotecan; Bev, bevacizumab; CALGB, Cancer and Leukemia Group B; Cap, capecitabine; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; GERCOR, Groupe d'Etude et de Recherche Clinique en Oncologie et Radiothérapie; HD, high dose; IFL, irinotecan; IFN, interferon alfa-2a; INT, Intergroup; LD, low dose; LEV, levamisole; LV, leucovorin; LVFU2, semimonthly fluorouracil and leucovorin; mFOLFOX6, modified FOLFOX; MOF, semustine, vincristine, and fluorouracil; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PVI, portal vein infusion; SWOG, Southwest Oncology Group; UFT, tegafur-uracil; XELOX, intravenous oxaliplatin plus oral capecitabine.

Table A2. External Validation of the Nomogram for 6-Month Mortality Using 3,227 Patients From Trial N0147

Patient Group	Actual Rate (95% CI)	Average Prediction	No. of Participants
Overall	0.0112 (0.0081 to 0.0154)	0.0119	3,227
Age, years			
< 70	0.0072 (0.0044 to 0.0111)	0.0094	2,765
≥ 70	0.0346 (0.0199 to 0.0556)	0.0275	462
PS			
0	0.0089 (0.0056 to 0.0134)	0.0106	2,472
1	0.0177 (0.0095 to 0.0301)	0.0161	735
≥ 2	0.0500 (0.0013 to 0.2487)	0.0264	20
Grade			
1	0.0073 (0.0015 to 0.0212)	0.0069	410
2	0.0094 (0.0057 to 0.0146)	0.0087	2,024
≥ 3	0.0177 (0.0097 to 0.0294)	0.0229	793
Lymph node ratio			
< 0.50	0.0104 (0.0070 to 0.0149)	0.0104	2,794
≥ 0.50	0.0162 (0.0065 to 0.0330)	0.0222	433
Tumor stage			
T1	0.0075 (0.0002 to 0.0412)	0.0034	133
T2	0.0112 (0.0031 to 0.0284)	0.0086	357
T3	0.0127 (0.0086 to 0.0180)	0.0119	2,367
T4	0.0027 (0.0001 to 0.0150)	0.0187	370

NOTE. Average predicted probabilities of 6-month mortality and actual 6-month mortality rates with exact binomial 95% CIs, presented overall and by patient subgroup defined by the nomogram. All average predictions fall within the exact 95% CIs for the actual rates, with the exception of tumor stage T4.
Abbreviation: PS, performance status.