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ORIGINAL REPORT

Clinical Calculator for Early Mortality in Metastatic Colorectal Cancer: An Analysis of Patients From 28 Clinical Trials in the Aide et Recherche en Cancérologie Digestive Database

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ABSTRACT

Purpose
Factors contributing to early mortality after initiation of treatment of metastatic colorectal cancer are poorly understood.

Materials and Methods
Data from 22,654 patients enrolled in 28 randomized phase III trials contained in the ARCAD (Aide et Recherche en Cancérologie Digestive) database were pooled. Multivariable logistic regression models for 30-, 60-, and 90-day mortality were constructed, including clinically and statistically significant patient and disease factors and interaction terms. A calculator (nomogram) for 90-day mortality was developed and validated internally using bootstrapping methods and externally using a 10% random holdout sample from each trial. The impact of early progression on the likelihood of survival to 90 days was examined with time-dependent Cox proportional hazards models.

Results
Mortality rates were 1.4% at 30 days, 3.4% at 60 days, and 5.5% at 90 days. Among baseline factors, advanced age, lower body mass index, poorer performance status, increased number of metastatic sites, *BRAF* mutant status, and several laboratory parameters were associated with increased likelihood of early mortality. A multivariable model for 90-day mortality showed strong internal discrimination (C-index, 0.77) and good calibration across risk groups as well as accurate predictions in the external validation set, both overall and within patient subgroups.

Conclusion
A validated clinical nomogram has been developed to quantify the risk of early death for individual patients during initial treatment of metastatic colorectal cancer. This tool may be used for patient eligibility assessment or risk stratification in future clinical trials and to identify patients requiring more or less aggressive therapy and additional supportive measures during and after treatment.

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INTRODUCTION

Randomized controlled clinical trials play a pivotal role of establishing new or improved cancer treatments within particular tumor types or patient populations, yet the rate of clinical trial participation among patients with cancer remains < 5%.[1] It would be valuable to be able to identify those patients at an increased risk of severe toxicity or early mortality, for whom receipt of treatment may be associated with greater risk than benefit and whose inclusion may obscure the assessment of treatment effect because they do not meet evaluation criteria for critical end points. For this reason, most cancer clinical trials limit enrollment to those patients who are expected to live at least 3 to 6 months beyond treatment initiation, with exact specifications depending on the specific disease under study.[2]

ASSOCIATED CONTENT

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

Variable	No.	Average	%
Age, years			
Mean (SD)		61 (11)	
Median (IQR)		62 (55-69)	
Missing	7		0
Sex			
Male	13,902		62
Female	8,622		38
Missing	18		0
Performance status			
0	11,966		53
1	9,483		42
2+	974		4
Missing	231		1
BMI			
Mean (SD)		26 (5)	
Median (IQR)		25 (23-29)	
Missing	1,533		7
Tumor location			
Colon	11,829		69
Rectum	5,035		29
Both	282		2
Missing	5,508		24
No. organs with metastases			
0-1	8,220		44
2	6,561		35
3	2,834		15
4+	900		5
Missing	4,139		18
Liver involvement			
Yes	14,441		78
No	4,100		22
Missing	4,113		18
Lung involvement			
Yes	6,657		37
No	11,260		63
Missing	4,737		21
Peritoneal involvement			
Yes	1,642		16
No	8,674		84
Missing	12,338		54
LN involvement			
Yes	6,157		39
No	9,660		61
Missing	6,837		30
Prior chemotherapy			
Yes	4,313		21
No	16,153		79
Missing	2,188		10
KRAS			
Mutant	3,025		38
Wild type	4,885		62
Missing	14,744		65
BRAF			
Mutant	387		8
Wild type	4,423		92
Missing	17,844		79
WBC count, $\times 10^9$/L			
Mean (SD)		8.4 (3.4)	
Median (IQR)		7.8 (6.3-9.7)	
Missing	4,436		20
ANC, $\times 10^9$/L			
Mean (SD)		5.7 (2.7)	
Median (IQR)		5.1 (3.9-6.8)	
Missing	6,497		29
dNLR			
Mean (SD)		2.4 (1.4)	
Median (IQR)		2.1 (1.5-2.8)	
Missing	8,532		38
Platelets, $\times 10^9$/L			
Mean (SD)		335 (128)	
Median (IQR)		310 (245-398)	
Missing	1,887		8
Hemoglobin, g/dL			
Mean (SD)		12.4 (1.7)	
Median (IQR)		12.4 (11.2-13.6)	
Missing	7,691		34
Bilirubin, mg/dL			
Mean (SD)		0.63 (0.94)	
Median (IQR)		0.50 (0.34-0.69)	
Missing	3,010		13
Treatment class			
Targeted	9,710		43
Nontargeted	12,944		57
Missing	0		0
Targeted Rx type			
Anti-ANG	6,177		64
Anti-EGFR	2,646		27
Both	887		9
Not applicable	12,944		49
Death by 30 days			
Yes	298		1.3
No	22,356		98.7
Missing	0		0
Death by 60 days			
Yes	761		3.4
No	21,823		96.6
Missing	70		0.3
Death by 90 days			
Yes	1,234		5.5
No	21,290		94.5
Missing	130		0.6

(continued in next column)

(continued from previous column)

Abbreviations: ANC, absolute neutrophil count; ANG, angiogenic; BMI, body mass index; dNLR, derived neutrophil-to-lymphocyte ratio; EGFR, epidermal growth factor receptor; IQR, interquartile range; LN, lymph node; Rx, treatment; SD, standard deviation.

Assessment of patient prognosis is inherently subjective, however, and often requires the treating physician to consider an array of patient and disease factors that may be clinically challenging to synthesize.

Within metastatic colorectal cancer (mCRC), the relative contribution of commonly measured patient and disease characteristics to a given individual's likelihood of early mortality, and whether or how these features may interact, remains poorly understood. McPhail et al[3] conducted a population-based analysis of early mortality (defined by the authors as death within 1 year of diagnosis) among all patients diagnosed with breast, colorectal, lung, prostate, or ovarian cancers in England in 2012 and found age, stage of disease at diagnosis, income, and geographic location to be independent predictors of mortality. A similar analysis limited to patients diagnosed with colorectal cancer in England between 2006 and 2008 found that approximately 33% of patients diagnosed with colon cancer and 25% of patients with rectal cancer die within 1 year of diagnosis, with advanced age, later stage at diagnosis, deprivation, and emergency presentation associated

with an increased likelihood of early death. However, relative rather than absolute risks of early mortality by initial stage of disease were presented by the authors, such that the empiric death rate among patients with metastatic disease alone could not be assessed.[4] Furthermore, mortality by time points earlier than 1 year was not reported. Lieu et al[5] and Renfro et al[6] reported that extreme (young or old) age and low body mass index (BMI), respectively, were associated with poorer survival in an ARCAD (Aide

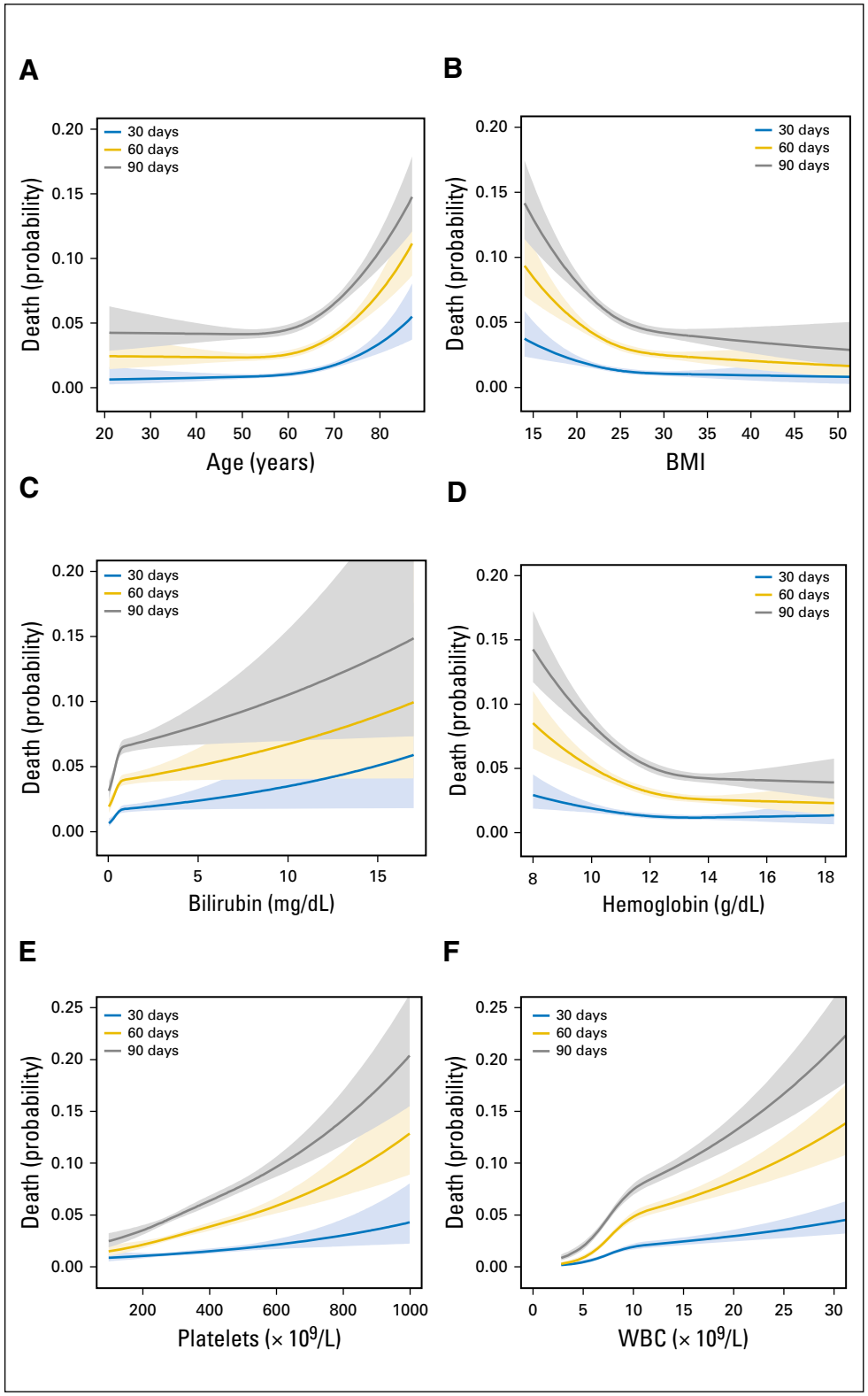

Fig 1. Nonlinear continuous univariable effects of (A) age, (B) body mass index (BMI), (C) bilirubin, (D) hemoglobin, (E) platelets, (F) WBC count, (G) absolute neutrophil count (ANC), and (H) derived neutrophil-to-lymphocyte ratio (dNLR) on early mortality at 30, 60, and 90 days. Shaded gray regions are 95% confidence bands.

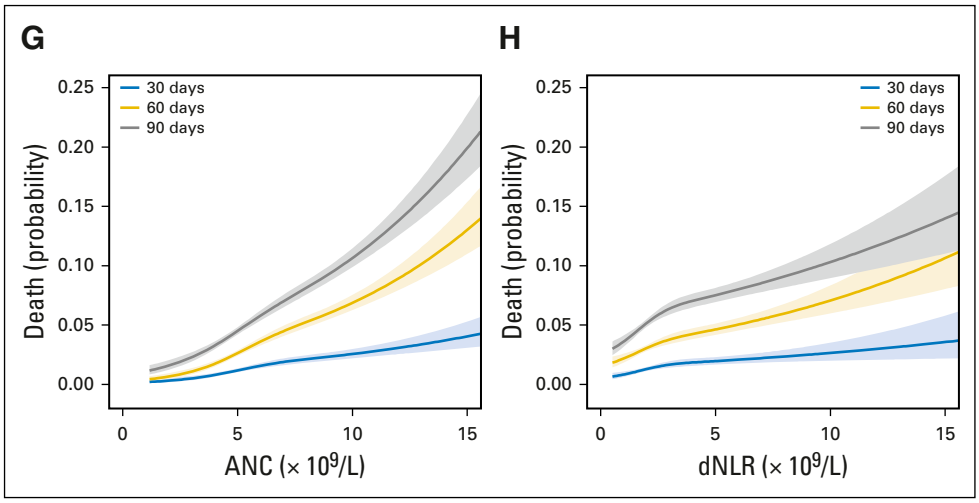

Fig 1. (Continued).

et Recherche en Cancérologie Digestive) analysis of patients enrolled in clinical trials of first-line treatment of mCRC, although early mortality was not a focus of these analyses. Shibutani et al[7] suggested that pretreatment albumin to globulin ratio may predict survival and response to chemotherapy in unresectable mCRC, but likewise did not examine early mortality. Köhne et al[8] and Chibaudel[9] developed risk scoring systems to predict overall survival in patients receiving front-line treatment of mCRC; however, again, neither tool specifically examined early mortality and each was based on far fewer patients than are presently available in the ARCAD database.

In addition to limited knowledge of prognostic factors associated with early mortality in mCRC, to our knowledge, clinical tools for predicting the likelihood of early mortality for a given patient do not currently exist for this patient population, although one such tool was recently developed for early-stage colon cancer.[10] Because overall survival can be highly variable in metastatic disease, the ability to objectively determine information about an individual patient's disease status and clinical characteristics and use these to construct an individualized prediction of the likelihood of 90-day survival could serve two key purposes: identification of patients requiring aggressive supportive care during initial therapy and improved patient selection processes for ongoing and future clinical trials.

To improve our collective understanding of prognostic factors related to early mortality in mCRC, we pooled individual patient data from > 20,000 individuals enrolled in 28 randomized front-line clinical trials and identified factors (directly or differentially) associated with early mortality. We then used these factors to develop a tool for clinical assessment of patients being considered for participation in first-line trials for mCRC.

MATERIALS AND METHODS

Description and Purpose of the ARCAD Database

The ARCAD database contains individual data on > 20,000 patients enrolled in 28 randomized front-line trials in mCRC since 1997 (Appendix Table A1, online only). The ARCAD collaborative group was originally established to study end points such as progression-free survival as candidate surrogates for overall survival, and since then it has also produced a number of major analyses to improve understanding of this disease.[5,6,11]

Statistical Methods

Descriptive statistics for patient, disease, and treatment characteristics as well as mortality rates at each time point of interest (30, 60, 90 days) were computed, and rates of missing data reported. For prognostic modeling, patient factors collected at the time of randomization were evaluated for possible associations with early mortality including age; sex; performance status (PS; 0, 1, 2+); BMI; *BRAF* or *KRAS* status (mutant [MT] *v* wild type [WT]); number of metastatic sites, counted as number of affected organs (0 or 1, 2, 3, 4+); presence versus absence of liver, lung, peritoneal, and lymph node metastases; prior chemotherapy (yes, no); baseline bilirubin, hemoglobin, platelets, WBC count, absolute neutrophil count (ANC), derived neutrophil to lymphocyte ratio (dNLR);[12,13] treatment class (targeted *v* nontargeted); and targeted treatment type (antiangiogenic *v* anti–epidermal growth factor receptor). Missing baseline data were accounted for via multiple imputation; specifically, bootstrapped regression with predictive mean matching was used to maintain a level of variability in the imputed data similar to what exists in the available data.[14,15] Outcome data (mortality and progression times) were not imputed. Some variables of interest, such as side of primary tumor (right *v* left) were excluded from consideration in this analysis because values were missing for > 50% of patients, with the most common reason for unavailable data being that these items were not collected by some trials.

To quantify the impact of baseline prognostic factors on the likelihood of early mortality, logistic regression models with single predictor variables of interest were fit to identify significant predictors of mortality at each time point, where significance required both $P < .05$ and clinically meaningful effects (odds ratios [ORs]). In models containing continuous variables, restricted cubic splines[14,15] were used to test for possible nonlinearity of the effects on the log odds scale. When significant ($P < .05$) nonlinearity (such as U-shaped risk of early mortality) as a function of a given candidate variable was found, the effect curve was plotted on the probability scale with 95% confidence bands for visual inspection, and spline modeling was subsequently carried forward in multivariable models; otherwise, standard linear modeling was subsequently used. Two-way interactions were tested between significant independent variables, where $P < .01$ for both the interaction effect and clinically differentiable effects (ORs or curves) across factor levels indicated significance. Statistically and clinically significant variables were then carried forward to multivariable logistic regression models for each time point; variables no longer contributing either statistically or clinically on statistical adjustment were then excluded, resulting in final multivariable models for each time point.

Finally, a nomogram (calculator) was developed from the final multivariable model for mortality within 90 days of protocol enrollment. As measures of internal validation, the concordance index (C-index; equivalent to the area under the receiver operating characteristic curve) and a bootstrapping-based calibration plot of actual versus predicted outcomes were reported, where the latter contained a nonparametrically smoothed curve representing the functional relationship between actual versus predicted outcomes over risk groups.[14,15] External validation of the nomogram was performed using a 10% random holdout sample from each trial; because of the rarity of early mortality events within any individual trial, it was deemed not feasible to conduct external validation using any single separate trial. Disease progression (as a time-varying variable) was excluded from consideration in final models, because progression status is generally unknown at the time when the tool being developed here is intended for use. Analyses were performed using the R project for statistical computing (http://www.R-project.org).

RESULTS

Descriptive Statistics

A total of 22,654 patients enrolled in 28 ARCAD trials were analyzed (Appendix Table A1). Across these trials, the median length of follow-up among living patients is 19 months. Baseline patient demographics and disease characteristics are summarized in Table 1. The mean age was 61 years, 62% of patients were male, 53% had an Eastern Cooperative Oncology Group performance status of 0, 69% had primary tumors in the colon only, and 21% had received prior chemotherapy. Early mortality rates were as follows: 1.4% at 30 days, 3.4% at 60 days, and 5.5% at 90 days.

Table 2. Empirical (unadjusted) Probabilities of Early Mortality and Multivariable (adjusted) ORs, 95% CIs, and *P* Values for Early Mortality at Each Time Point, on the Basis of the Construction Data Set (N = 22,654)

Variable	30 Days			60 Days			90 Days		
	Rate	OR (95% CI)	*P*	Rate	OR (95% CI)	*P*	Rate	OR (95% CI)	*P*
Age, years			< .001			< .001			< .001
50	0.008	–		0.023	–		0.041	–	
60	0.010	1.54 (1.13 to 2.10)		0.026	1.22 (0.98 to 1.51)		0.045	1.19 (0.99 to 1.42)	
70	0.017	2.34 (1.72 to 3.19)		0.041	1.87 (1.52 to 2.28)		0.065	1.68 (1.42 to 2.00)	
80	0.034	3.55 (2.50 to 5.04)		0.074	3.19 (2.46 to 4.13)		0.106	2.59 (2.08 to 3.22)	
BMI			< .001			< .001			< .001
15	0.034	2.91 (1.72 to 4.90)		0.085	2.94 (2.06 to 4.19)		0.107	2.70 (2.01 to 3.60)	
20	0.020	1.80 (1.28 to 2.52)		0.050	1.88 (1.49 to 2.37)		0.080	1.80 (1.49 to 2.19)	
30	0.011	–		0.025	1.08 (0.87 to 1.34)		0.042	1.10 (0.91 to 1.31)	
40	0.009	1.02 (0.56 to 1.82)		0.020	–		0.035	–	
PS			< .001			< .001			< .001
0	0.008	–		0.017	–		0.028	–	
1	0.017	1.56 (1.18 to 2.04)		0.044	1.92 (1.60 to 2.31)		0.074	1.96 (1.69 to 2.27)	
2+	0.050	3.02 (2.05 to 4.47)		0.134	4.37 (3.37 to 5.67)		0.201	4.38 (3.52 to 5.44)	
BRAF			< .001			< .001			< .001
WT	0.011	–		0.028	–		0.046	–	
MT	0.043	3.78 (2.88 to 4.98)		0.090	3.18 (2.62 to 3.86)		0.148	3.52 (3.01 to 4.12)	
No. metastasis sites			< .001			< .001			< .001
0-1	0.010	–		0.025	–		0.043	–	
2	0.015	1.49 (1.11 to 1.98)		0.034	1.26 (1.04 to 1.52)		0.054	1.22 (1.05 to 1.41)	
3	0.020	1.92 (1.37 to 2.68)		0.048	1.71 (1.37 to 2.13)		0.076	1.66 (1.39 to 1.98)	
4+	0.026	2.24 (1.41 to 3.56)		0.062	1.97 (1.45 to 2.68)		0.106	2.13 (1.67 to 2.71)	
Bili, mg/dL			< .001			< .001			< .001
1	0.017	–		0.040	–		0.066	–	
5	0.024	1.47 (0.94 to 2.29)		0.050	1.26 (0.90 to 1.77)		0.081	1.24 (0.94 to 1.65)	
10	0.035	2.38 (1.09 to 5.18)		0.067	1.69 (0.91 to 3.12)		0.105	1.63 (0.97 to 2.72)	
15	0.051	3.85 (1.19 to 12.0)		0.089	2.26 (0.89 to 5.60)		0.135	2.13 (0.98 to 4.52)	
WBC count, $\times 10^9$/L			< .001			< .001			< .001
5	0.005	–		0.009	–		0.021	–	
10	0.019	2.67 (1.93 to 3.70)		0.049	2.31 (1.83 to 2.91)		0.075	1.74 (1.43 to 2.11)	
15	0.025	3.39 (2.44 to 4.71)		0.065	2.71 (2.11 to 3.49)		0.101	2.01 (1.63 to 2.49)	
20	0.030	4.19 (2.95 to 5.95)		0.082	3.11 (2.32 to 4.15)		0.132	2.30 (1.79 to 2.94)	
dNLR			.0046						
1	0.008	–							
5	0.020	1.74 (1.25 to 2.41)							
10	0.026	1.88 (1.23 to 2.88)							
15	0.036	2.04 (1.09 to 3.80)							
ANC, $\times 10^9$/L						< .001			< .001
1				0.004	–		0.012	–	
5				0.026	1.43 (1.16 to 1.78)		0.045	1.42 (1.19 to 1.70)	
10				0.069	2.29 (1.80 to 2.92)		0.106	2.24 (1.82 to 2.75)	
15				0.130	3.64 (2.59 to 5.11)		0.199	3.51 (2.62 to 4.69)	

NOTE. Age, BMI, and laboratory values are modeled as continuous and nonlinear on the log odds scale. The dash (–) indicates the reference group with lowest risk. Variables not contributing significantly to at least one time point's model after adjustment are excluded.

Abbreviations: ANC, absolute neutrophil count; Bili, bilirubin; BMI, body mass index; dNLR, derived neutrophil-to-lymphocyte ratio; MT, mutant; OR, odds ratio; PS, performance status; WT, wild type.

Univariable and Pairwise Interaction Models for Early Mortality

In the construction data set (N = 20,397), age was associated with early mortality at every time point ($P < .001$), and, in each case, the risk of early death was found to increase with age in a nonlinear fashion on the log-odds scale (Fig 1A). BMI was also significantly associated with early mortality at each time point ($P < .001$), with the highest risk of death observed in the cohort with the lowest BMI and decreasing risk according to a nonlinear function for patients with higher BMI (Fig 1B). 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; 90-day PS1/PS0 OR, 2.71; PS2+/PS0 OR, 8.62). *BRAF* MT (*v* WT) status was associated with increased likelihood of early mortality at each time point ($P < .001$ for 30, 60, and 90 days; 90-day MT/WT OR, 3.62), whereas prior receipt of chemotherapy for any reason was associated with decreased likelihood of early mortality at each time point (30-day OR, 0.66; $P = .01$; 60-day OR, 0.67; $P < .001$; 90-day OR, 0.76; $P < .001$). Having more metastatic sites was significantly associated with increased likelihood of early mortality at all time points ($P < .001$ for 30, 60, and 90 days, with 90-day ORs of 1.28, 1.83, and 2.65 for 2, 3, and 4 *v* 0 or 1 metastatic site, respectively). At all time points, presence of peritoneal metastases was further associated with an increased likelihood of early mortality (30-day OR, 1.75; $P < .001$; 60-day OR, 1.59; $P < .001$; 90-day OR, 1.64; $P < .001$), and metastasis to distant lymph nodes was also associated with early mortality at 90 days (90-day OR, 1.28; $P < .001$). All baseline laboratory values that were considered (bilirubin, hemoglobin, platelets, WBC count, ANC, and dNLR) were associated with early mortality at all time points (*P* values ranging from < .001 to .0041), some via nonlinear relationships, as shown in Figures 1C-1H. Patient sex, *KRAS* status, tumor location (colon *v* rectum), and presence of liver or lung metastases were not significantly associated with early mortality at any time point. Among trials with concurrent randomization, class of therapy (targeted *v* nontargeted) was not associated with early mortality. No pairwise interactions showed both statistical and clinical significance on visual inspection at any time point.

Multivariable Analyses for Early Mortality

Final multivariable models retaining statistically and clinically relevant terms after adjustment are shown in Table 2. In the final multivariable model for mortality by 30 days, increased age ($P < .001$), decreased BMI ($P < .001$), worse PS ($P < .001$), *BRAF* MT status ($P < .001$), increased number of metastatic sites ($P < .001$), increased bilirubin ($P < .001$), increased WBC count ($P < .001$), and increased derived neutrophil-to-lymphocyte ratio (dNLR) ($P = .0046$) were associated with an increased likelihood of early death. The final multivariable models for mortality by 60 and 90 days were similar, with increased ANC rather than increased dNLR showing a significant association with early mortality ($P < .001$ in both models).

Nomogram for 90-Day Mortality: Internal Validation

The final multivariable model for mortality by 90 days showed strong internal validity, with a discrimination C-index of 0.772 indicating a 72.2% correct model identification of the higher-risk patient across all possible pairs of patients. Furthermore, the final model for mortality by 90 days demonstrated good internal calibration of observed versus predicted outcomes across a spectrum of risk groups, 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 early mortality by 90 days can be computed (see Appendix, online only, for nomogram instructions).

Nomogram for 90-Day Mortality: External Validation

External validation results for the final 90-day model are shown in Table 3. A total of 2,230 patients with known survival status at 90 days composed the validation cohort, representing a 10% holdout sample from each trial. Of these patients, 127 (5.7%; 95% CI, 4.8% to 6.8%) died by 90 days, with the average model-predicted rate of 5.0% falling within the 95% CI for the actual rate. In addition, within each patient subgroup (defined by levels of each variable in the final model), the average predicted rate fell within the corresponding 95% interval for the actual rate with just one exception: the subgroup of patients with four or more metastatic sites had a lower mortality rate (4.0%: 95% CI, 2.3% to 6.8%) than the predicted rate (8.7%) for that group.

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 61 years old with BMI of 20, PS of 0, *BRAF* WT status, one metastatic site, bilirubin of 0.5 mg/dL, WBC count of 8.0×10^9/L, and ANC of 6.0×10^9; patient B is 79 years old with BMI of 30, PS of 1, *BRAF* MT status, three metastatic sites, bilirubin of 1.9 mg/dL, WBC count of 12.0×10^9, and ANC of 9.0×10^9. Our model predicts that patient A has a 2.5% chance of early death by 90 days (95% CI, 2.0% to 3.0%), and patient B has a 42% chance of early death (95% CI, 36% to 48%). That is, the risk of early mortality for patient B is predicted to be 16.8 times the risk for patient A.

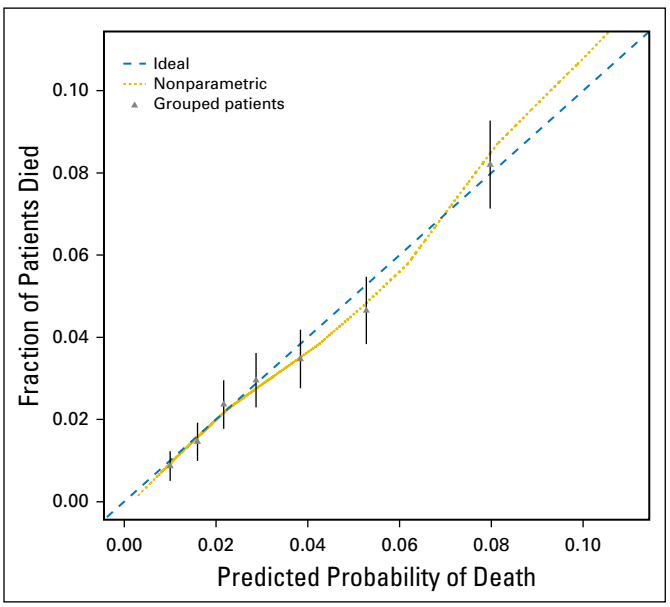

Fig 2. Calibration of the nomogram for 90-day mortality.

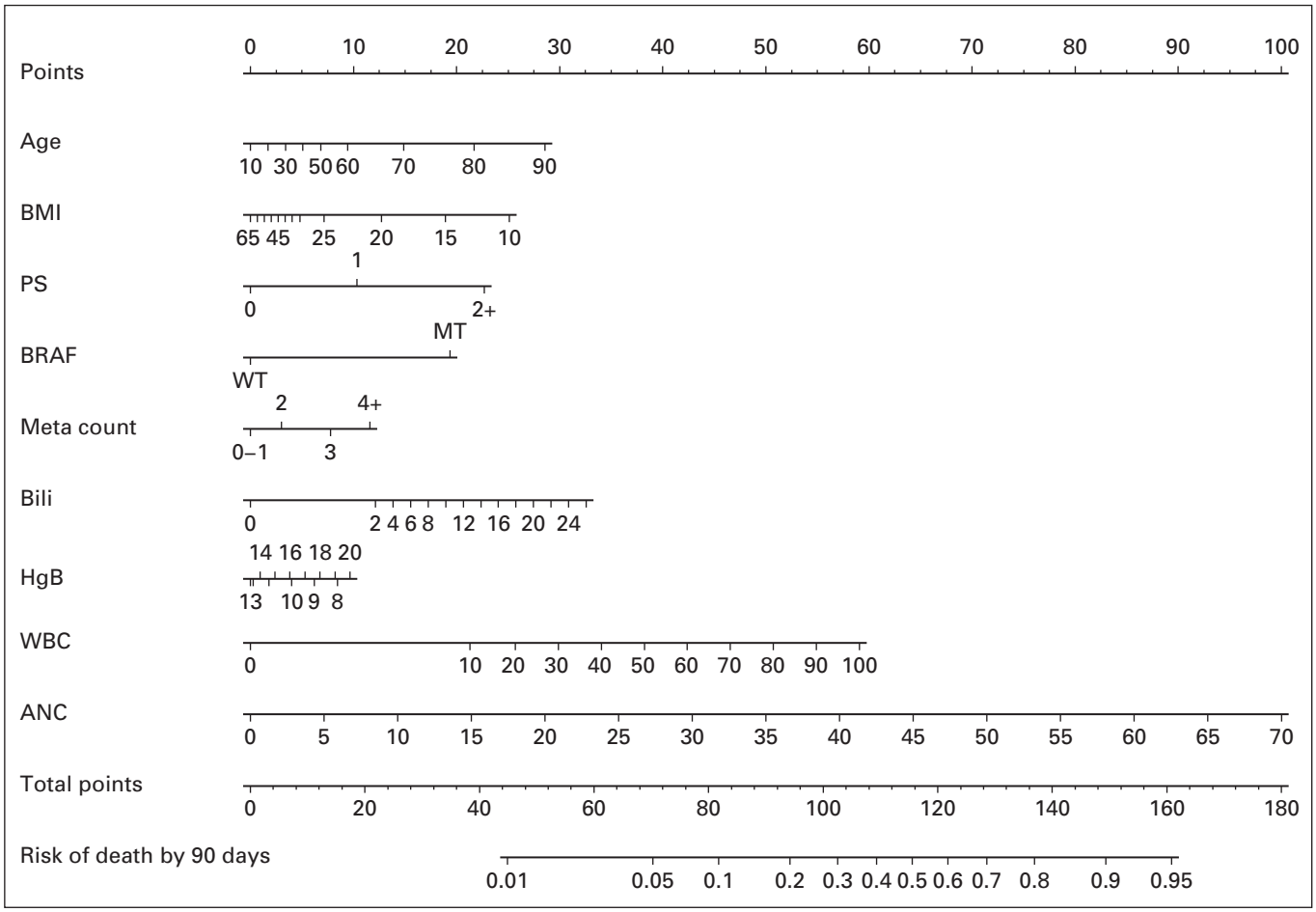

Fig 3. Nomogram for 90-day mortality. ANC, absolute neutrophil count; Bili, bilirubin; BMI, body mass index; HgB, hemoglobin; Meta count, number of metastatic organs involved; MT, mutant; PS, ECOG/WHO Performance Status; WT, wild type.

DISCUSSION

In this pooled analysis of > 22,000 patients from 28 randomized clinical trials of front-line treatment in mCRC, 5.5% of patients had died within 90 days after being randomly assigned. When factors contained in the ARCAD database were investigated, we found that increased age, decreased BMI, worsened PS, a greater number of metastatic sites, *BRAF* MT status, and elevated laboratory markers collectively representing an inflammatory response were associated with an increased likelihood of death in the first 90 days, whereas *KRAS* status, patient sex, individual sites of metastases, location of primary tumor (colon *v* rectum), and prior chemotherapy use did not seem to play an early prognostic role.

To support identification of patients with a dramatically increased likelihood of early mortality, we constructed and validated a nomogram to aid clinical prognostication and facilitate individualized evaluation of patients with advanced disease. We anticipate that this calculator will be especially useful in confirming patient eligibility for future clinical trials and limiting enrollment to patients whose likelihood of survival beyond 90 days is reasonably high, such that the effect of experimental treatments on clinical outcomes may be evaluated more clearly and with less attrition due to early deaths. In addition, patients identified as at high risk of short-term mortality could be managed with more- or less-intensive therapy, depending on patient preferences and joint patient-physician decision making, as well as offered enhanced supportive care if they are to be treated outside the auspices of a clinical trial. A tool that allows clinicians to stratify patients according to risk of early death more effectively could also aid in developing trials focusing on supportive care needs in the population of patients with poor prognosis, potentially affecting both quantity and quality of life. Significantly, we may then start to identify therapeutic strategies that may be more harmful to patients and thus tailor the results of trials into clinical practice in a more individualized manner.

There are some limitations to our work. First, among the trials considered, we were unable to reliably distinguish between early deaths due to documented progression versus deaths potentially related to treatment toxicity, without making broad assumptions that may have been misleading. For this reason, throughout, we focus on purely prognostic analyses of factors known at baseline (time of randomization). Second, although location of primary tumor (right *v* left) has recently been identified as a prognostic (and perhaps predictive) factor in the metastatic disease setting,[16,17] we were unable to assess this factor in the present analysis of early mortality, because tumor sidedness was only noted in a small minority of trials, precluding imputation of missing data.

Table 3. External Validation of the Nomogram for 90-Day Mortality Using a 10% Holdout Sample From Each Trial (n = 2,230)

Patient Group	Average Predicted Rate	Actual Rate	95% CI for Actual Rate	No.
Overall	0.050	0.057	0.048 to 0.068	2,230
Age, years				
< 70	0.043	0.047	0.038 to 0.068	1,706
70+	0.072	0.088	0.066 to 0.012	524
BMI				
< 30	0.052	0.059	0.049 to 0.071	1,853
30+	0.039	0.048	0.029 to 0.076	377
PS				
0	0.028	0.040	0.028 to 0.053	1,186
1	0.065	0.066	0.051 to 0.84	955
2+	0.182	0.191	0.118 to 0.291	89
BRAF				
WT	0.041	0.046	0.037 to 0.057	2,013
MT	0.131	0.161	0.116 to 0.219	217
No. metastasis sites				
0-1	0.039	0.047	0.035 to 0.062	965
2	0.049	0.054	0.040 to 0.072	820
3	0.072	0.069	0.045 to 0.102	349
4+	0.087	0.040	0.023 to 0.068	96
Bili, mg/dL				
< 1.9	0.050	0.056	0.047 to 0.066	2,202
1.9+	0.064	0.143	0.047 to 0.336	28
WBC count, $\times 10^9$/L				
< 10.0	0.039	0.042	0.033 to 0.053	1,697
10.0+	0.086	0.105	0.081 to 0.135	533
ANC, $\times 10^9$/L				
< 8.0	0.041	0.045	0.036 to 0.055	1,918
8.0+	0.104	0.131	0.097 to 0.175	312

NOTE. Average predicted probabilities of 90-day mortality and actual 90-day mortality rates with 95% exact binomial confidence intervals, presented overall and by patient subgroups defined by the nomogram.
Abbreviations: ANC, absolute neutrophil count; Bili, bilirubin; BMI, body mass index; MT, mutant; PS, performance status; WT, wild type.

Similarly, laboratory markers including serum lactate dehydrogenase, carcinoembryonic antigen, and C-reactive protein were not considered, because sparse data collection and nonstandardized assays across trials made their inclusion infeasible. We also note that our findings are only applicable to patients with advanced colorectal cancer about to initiate front-line therapy and, more specifically, those who might also meet the eligibility criteria for participation in our clinical trials. To the degree that a patient encountered in practice has worse performance status or additional comorbidities than a typical trial-eligible patient, the probabilities of early mortality presented here may be viewed as best-case scenario at the treating physician's discretion. Despite these theoretical limitations, the present validated tool, on the basis of patient-level data from 28 major randomized clinical trials, will prove useful for trial eligibility screening and patient stratification as well as identification of patients in clinical practice who may benefit from more or less aggressive treatment.

In summary, the rate of early mortality by 90 days across 28 first-line trials conducted in patients with mCRC was 5.5%, with several patient and disease factors showing strong associations with increased or decreased likelihood of this outcome. A validated clinical nomogram taking these characteristics into account may be potentially useful for quantifying the risk of early death for individual patients, thus informing discussions between clinicians and patients as well as supporting the prognostic homogeneity of cohorts of patients enrolled to future clinical trials.

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Appendix

Instructions for Use of the Nomogram for 90-Day Mortality

First, risk points associated with each variable are obtained via vertical translation of the patient's variable value (eg, BRAF MT) to the scale labeled "Points" in the nomogram (ie, BRAF mutation contributes 20 points to 90-day mortality risk). Next, the points associated with each variable value for the patient are totaled across the variables measured. This total is then located on the scale "Total Points" and then vertically mapped to obtain the predicted probability of early mortality by 90 days (eg, 100 total points corresponds to a predicted probability of approximately 27%).

Table A1. ARCAD Trials Used in Early Mortality Analyses

Trial	Years Accrued	Front-Line Treatment Arm(s)	N
03-TTD-01	2002-2004	FUOX *v* CAPOX	340
AGITG (MAX)	2005-2007	Capecitabine *v* capecitabine plus bevacizumab *v* capecitabine plus bevacizumab plus mitomycin	471
AIO22	2002-2004	FUFOX *v* CAPOX	469
AVF2107g	2000-2002	IFL *v* IFL plus bevacizumab	919
AVF2192g	2000-2002	5-FU *v* 5-FU plus bevacizumab	207
BICC-C	2003-2004	mIFL plus or minus bevacizumab *v* FOLFIRI plus or minus bevacizumab *v* CapIRI	535
C97-3	1997-1999	FOLFOX6 *v* FOLFIRI	222
CAIRO	2003-2004	Capecitabine *v* CapIRI	820
CAIRO2	2005-2006	CAPOX plus bevacizumab *v* CAPOX plus bevacizumab plus cetuximab	747
COIN	2005-2008	FOLFOX *v* FOLFOX plus cetuximab *v* intermittent FOLFOX	2,430
CRYSTAL	2004-2005	FOLFIRI plus cetuximab *v* FOLFIRI	1,212
FIRE II	2004-2006	XELOX plus cetuximab *v* CapIRI plus cetuximab	177
FIRE III	2007-2012	FOLFIRI plus bevacizumab *v* FOLFIRI plus cetuximab	589
FOCUS	2000-2003	5-FU *v* 5-FU plus oxaliplatin *v* 5-FU plus irinotecan	2,118
FOCUS II	2004-2006	5-FU *v* FOLFOX *v* capecitabine *v* CAPOX	456
GONO	2001-2005	FOLFOXIRI *v* FOLFIRI	244
HORG 99.30	2000-2004	FOLFOXIRI *v* FOLFIRI	283
HORIZON II	2006-2010	FOLFOX plus CAPOX plus cediranib *v* FOLFOX plus CAPOX	1,065
HORIZON III	2006-2009	FOLFOX plus cediranib *v* FOLFOX plus bevacizumab	1,584
MACRO	2006-2008	XELOX plus bevacizumab *v* bevacizumab	475
N016966	2004-2005	FOLFOX plus CAPOX plus bevacizumab *v* FOLFOX plus CAPOX	2,017
N9741	1999-2001	IFL *v* FOLFOX *v* IROX	1,415
OPTIMOX 1	2000-2002	FOLFOX4 *v* FOLFOX7	621
OPTIMOX 2	2004-2006	mFOLFOX7 *v* mFOLFOX7	202
OPUS	2005-2006	FOLFOX4 *v* FOLFOX4 plus cetuximab	338
PACCE (C249)	2005-2006	Chemotherapy plus bevacizumab *v* chemotherapy plus bevacizumab plus panitumumab	1,018
PRIME (C203)	2006-2008	FOLFOX *v* FOLFOX plus panitumumab	1,173
TRIBE	2008-2011	FOLFIRI plus bevacizumab *v* FOLFOXIRI plus bevacizumab	507
Total ARCAD			22,654

NOTE. Trials in italics had concurrent targeted *v* non-targeted randomization.

Abbreviations: AGITG, Australasian Gastro-Intestinal Trials Group; AIO, Arbeitsgemeinschaft Internistische Onkologie; ARCAD, Aide et Recherche en Cancérologie Digestive; AVF, anastomotic-vaginal fistula; BICC, Breast Cancer in City and Country; CAIRO, Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer; CapIRI, capecitabine and irinotecan; CAPOX, capecitabine plus oxaliplatin; COIN, Combination Chemotherapy With or Without Cetuximab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer; CRYSTAL, Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer; FIRE II, Cetuximab Plus Capecitabine and Irinotecan Compared With Cetuximab Plus Capecitabine and Oxaliplatin As First-Line Treatment for Patients With Metastatic Colorectal Cancer; FIRE III, FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First-Line Treatment of Colorectal Cancer; FOCUS, Fluorouracil, Oxaliplatin, and CPT11 Use and Sequencing; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; FUFOX, fluorouracil plus oxaliplatin; FUOX, continuous-infusion high-dose fluorouracil plus oxaliplatin; GONO, Gruppo Oncologico Nord Ovest; HORG, Hellenic Oncology Research Group; HORIZON II, Cediranib (AZD2171, RECENTIN) in Addition to Chemotherapy in Patients With Untreated Metastatic Colorectal Cancer; HORIZON III, First-Line Metastatic Colorectal Cancer Therapy in Combination With FOLFOX; IFL, irinotecan, leucovorin, and fluorouracil; IROX, irinotecan and oxaliplatin; m, modified; MACRO, Maintenance in Colorectal Cancer; OPTIMOX 1, a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study; OPTIMOX 2, Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer; PACCE, Panitumumab Advanced Colorectal Cancer Evaluation; PRIME, Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; TRIBE, Combination Chemotherapy and Bevacizumab As First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer; TTD, Tratamiento de los Tumores Digestivos; XELOX, capecitabine plus oxaliplatin; 5-FU, fluorouracil and leucovorin.