Simplified Prognostic Model in Patients with Oxaliplatin-Based or Irinotecan-Based First-Line Chemotherapy for Metastatic Colorectal Cancer: A GERCOR Study

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe prognostic factors in metastatic colorectal cancer.
2. Estimate prognostic score with a simple model using only PS and LDH as parameters.

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ABSTRACT

Background. The present study was done to establish a prognostic model for patients and trials using an oxaliplatin-based or irinotecan-based first-line chemotherapy in metastatic colorectal cancer.

Patients and Methods. Eight hundred three patients treated with FOLFOX or FOLFIRI in three prospective trials were randomly separated into learning ($n = 535$) and validation ($n = 268$) samples. Eleven baseline variables were evaluated in univariate and multivariate analysis as prognostic factors for overall survival, and a prognostic score was developed.

Results. Independent prognostic factors identified in multivariate analysis for overall survival were performance status (PS) ($p < .001$), serum lactate dehydrogenase (LDH) ($p < .001$), and number of metastatic sites ($p = .005$). A prognostic score based on these three vari-

ables was found efficient (Harrell's C index 0.61). This new model was improved by selecting only PS and LDH (Harrell's C index 0.64). Three risk groups for death could be identified: a low-risk group ($n = 184$; median overall survival [OS] 29.8 months), an intermediate-risk group ($n = 223$; median OS 19.5 months), and a high-risk group ($n = 128$; median OS 13.9 months). Median survival for the low-, intermediate-, and high-risk groups were 26.8, 21.1, and 16.5 months, respectively, in the validation sample (Harrell's C index 0.63).

Conclusions. Serum LDH level was the main prognostic factor in predicting survival, followed by WHO PS. We identified three risk groups for death depending on these two baseline parameters. This simple prognostic model can be useful for clinician's use and patient stratification in future clinical trials. *The Oncologist* 2011;16:1228–1238

INTRODUCTION

Colorectal cancer is the third most common cancer and the second cause of cancer death in the United States [1]. Consequently, metastatic colorectal cancer remains a major public health priority. Chemotherapy is the cornerstone treatment in the case of unresectable metastatic disease.

Heterogeneity in survival rates can be mainly explained by patient and tumor characteristics, host response factors, treatment strategy (drugs, regimen, surgery of metastasis). Of note, several prognostic factors have been found in previous clinical trials [2–15]. These were patient characteristics such as performance status (PS), age, sex, weight loss, biological variables such as white blood cell count (WBC), serum alkaline phosphatase (ALP) level, serum lactate dehydrogenase (LDH) level, serum carcino-embryonic antigen (CEA) level, or tumor characteristics like the number of metastatic sites or liver involvement (Table 1).

Three risk groups for death were recognized in patients receiving 5-fluorouracil-based chemotherapy for metastatic colorectal cancer, depending on four baseline prognostic parameters: PS, WBC count, ALP, and number of metastatic sites (Köhne model) [16]. The low-risk group was defined as patients with World Health Organization (WHO) PS 0–1 and 1 metastatic site. The intermediate-risk group was defined as patients with either WHO PS 0–1, >1 metastatic site, and ALP level <300 , or WHO PS >1 , 1 metastatic site, and WBC $<10,000/\text{mm}^3$. Finally, the high-risk group had either WHO PS 0–1, >1 metastatic site, and ALP level >300 , or WHO PS >1 , >1 metastatic site, and WBC $<10,000/\text{mm}^3$, or WHO PS >1 and WBC $>10,000/\text{mm}^3$. In recent trials, WHO PS and LDH level at baseline were strongly associated with survival (Table 1).

The aim of this study was (a) to identify prognostic factors in patients with metastatic colorectal cancer receiving an oxaliplatin-based or an irinotecan-based first-line chemotherapy, (b) to develop a prognostic scoring system based on the identified prognostic factors, and (c) to evaluate the efficiency of the previous model in this population.

PATIENTS AND METHODS

Trials

Individual patient data from three randomized trials including patients with previously untreated metastatic colorectal cancer were updated and pooled. The C97-3 study compared the FOLFIRI1 regimen as first-line chemotherapy until progression or limiting toxicity followed by the FOLFOX6 regimen as second-line therapy, to the reverse sequence [9].

The OPTIMOX1 study compared the FOLFOX4 regimen as first-line chemotherapy until disease progression or limiting toxicity, to an oxaliplatin stop-and-go strategy with 3 months of FOLFOX7 regimen followed by a maintenance therapy with simplified LV5FU2 until disease progression or 12 cycles, then reintroduction of the same FOLFOX7 regimen [11].

The OPTIMOX2 study compared the oxaliplatin stop-and-go strategy to a complete stop-and-go strategy after six cycles of modified FOLFOX7 regimen [17]. Of note, none of these trials used targeted therapies in combination with first-line chemotherapy.

Data

To be eligible, the Köhne model had to be applicable and the baseline LDH value had to be available. The following

Table 1. Prognostic factors for overall survival (*p*-value) in first-line metastatic colorectal cancer phase III trials (multivariate analysis)

Study	Reference	PS	LDH	ALP	No. sites	Adj therapy	CEA	WBC	Others
Rougier 1995	2	S	-	S	S	-	-	-	Liver Treatment Primary site and resection Prothrombin time
Giachetti 2000	3	S (.0001)	-	-	S (.0017)	-	-	-	Liver (.0013)
de Gramont 2000	4	S (.0001)	S (.0001)	S (.0062)	S (.0029)	-	-	-	Treatment (.0001)
Saltz 2000	5	S (<.001)	S (<.001)	-	S (<.001)	-	-	S (<.001)	Treatment (.03) Bilirubin (.005)
Hoff 2001	6	S (.0001)	-	S (.0001)	S (.0001)	-	-	-	Liver (.0035)
Van Cutsem 2001	7	S	-	S	S	-	-	-	Liver
Mitry 2004	8	S (.002)	- ^b	S (<.0001)	S (.04)	-	-	-	Weight loss (<.001) Treatment (.009)
Tournigand 2004	9	S (<.0001)	S (<.001)	S (<.0012)	S (.016)	S (.001)	S (.016)	-	Sex (.048) Liver (.016)
Colucci 2005	10	NS	-	-	S (.033)	-	-	-	
Tournigand 2006	11	S (<.0001)	S (<.0001)	S (<.0001)	S (.001)	-	-	-	Reintroduction of oxaliplatin (.032)
Giacchetti 2006	12	S (.003)	-	-	S (<.0001)	-	S (.01)	S ^a (.0002)	Analgesics (<.0001) CA 19-9 (.002) AST (.0005)
Souglakos 2006	13	S	-	-	-	NS	-	-	No tumor response (.0001)
Porschen 2007	14	S	-	S	-	-	-	S	Age
Falcone 2007	15	-	-	-	-	-	-	-	Liver (.005)

^a Granulocyte count.
^b LDH was not introduced in the multivariate analysis despite a strong association in univariate analysis ($p < .001$).
Abbreviations: -, not specified or not done; Adj therapy, adjuvant therapy; ALP, alkaline phosphatase; CEA, carcino-embryonic antigen; LDH, lactate dehydrogenase; No. sites, number of metastatic sites; NS, statistically not significant; PS, performance status; Ref, reference; S, statistically significant; WBC, white blood cell count.

data were analyzed for individual patients in all trials: patient identifier, center identifier, randomization date, treatment assigned by randomization, age, sex, performance status, primary tumor site (colon, rectum, or both), site of metastases, ALP level at baseline, LDH level at baseline, CEA level at baseline, date of first and last cycle of first-line chemotherapy, overall response status, date of first progression, progression status, survival status, and date of last news or death. Baseline WBC was available for patients with PS > 1 because it was required to calculate the Köhne score.

Statistical Considerations

Progression-free survival was defined as the time interval from randomization to first disease progression or death from any cause if disease progression did not occur. Alive

patients without progression were censored at the last follow-up. Progression was defined as assessed in each individual trial. Overall survival (OS) was defined as the time interval from randomization to death from any cause. Alive patients were censored at the last follow-up.

The median follow-up was estimated using the reverse Kaplan-Meier method [18]. Survival endpoints were estimated using the Kaplan-Meier method [19]. Patients were randomly separated with trial stratification into a learning sample (2/3) and a validation sample (1/3) to check overfitting [20].

The association between prognostic factors and survival was explored using univariate Cox analyses stratified on trials for all potential prognostic factors. Eleven baseline variables were evaluated in a univariate analysis: age (≤ 65 versus > 65), sex, PS (0 versus 1 versus 2), number of met-

Table 2. Patient characteristics

	Learning set (<i>n</i> = 535)		Validation set (<i>n</i> = 268)		<i>p</i>
	<i>n</i>	%	<i>n</i>	%	
Age: median [range]	65	[29–80]	64	[35–80]	ns
Sex: male versus female	315/220	59/41	170/98	63/37	ns
Primary site: colon versus rectum versus both (NA)	349/177/4 (5)	65/33/1 (1)	165/93/6 (4)	62/35/2 (1)	ns
Synchronous/metachronous (NA)	395/137 (3)	74/25 (1)	196/70 (2)	73/26 (1)	ns
Adjuvant chemotherapy: yes/no	101/434	19/81	57/211	21/79	ns
No. sites: 1 versus >1	311/224	58/42	152/116	57/43	ns
Liver involvement: yes/no	401/134	75/25	191/77	71/29	ns
PS: 0 versus 1 versus 2	290/215/30	54/40/6	163/116/15	61/43/6	ns
LDH: <i>N</i> versus >1 × ULN	283/252	53/47	136/132	51/49	ns
ALP: <i>N</i> versus 1–3 × ULN versus >3 × ULN (NA)	299/185/47 (4)	56/34/9 (1)	144/95/24 (5)	54/35/9 (1)	ns
CEA: <i>N</i> versus >1 × ULN (NA)	96/409 (30)	18/76 (6)	63/195 (10)	23/73 (4)	ns

Abbreviations: ALP, alkaline phosphatase; CEA, carcino-embryonic antigen; LDH, lactate dehydrogenase; NA, not available; ns, not significant; PS, performance status; ULN, upper limit of normal.

astatic sites (1 versus >1), liver involvement (yes versus no), primitive tumor (colon versus rectum versus both), synchronous versus metachronous disease, prior adjuvant chemotherapy (yes versus no), serum LDH level, serum ALP level, and serum CEA level. These variables were treated as qualitative data using cutoff for continuous variables in anticipation of elaborating a practical clinical tool. The Köhne scoring system was also explored. WBC was not considered for univariate and multivariate analysis because it was not available for all patients. Proportional hazards assumption was graphically assessed. Factors were considered for inclusion in the model as potentially associated with OS if the univariate *p* value was ≤.05. The Cox regression model stratified on trials was used for multivariate analysis of prognostic factors for OS [21].

A prognostic score was developed based on the identified prognostic factors in the multivariate analysis. The prognostic value for a given patient was the combination of the different variables weighted with the regression coefficients included in the multivariate analysis. To establish a practical and easy-to-compute score, the score was calibrated so that each variable contributed 1 or 2 units. The score was then calculated for each patient by adding the points corresponding to each prognostic factor retained in the multivariate model. The predictive accuracy of the new scoring system was examined and compared to the Köhne scoring system by calculating Harrell's C discrimination index extended for survival data [22]. Results of Harrell's C index vary from 0.5 (no discrimination for predicting OS) to 1.0 (perfect discrimination). Calibration was checked based on plotting results for patients with similar risk score

categories (high risk /intermediate risk/low risk) and thus compared the mean predicted probability with the mean observed outcome (i.e., OS at 36 months) [23]. Bootstrap (*n* = 150) was used to take into account overfitting regarding prediction and Harrell's C index. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) and STATA 11.0 (StataCorp LP, College Station, TX) software or R software (2.13.0, Design package).

RESULTS

Population

Among the 1,042 patients included in the three original trials, 803 were eligible. LDH values at baseline were not available in 134 patients, and the Köhne model could not be applied for 105 additional patients (WBC not available in 29 patients, number of metastatic sites not available for 2 patients, and ALP value not available for 74 patients).

The characteristics of the 803 studied patients were similar across trials (supplemental online Table 1). The patient characteristics in learning sample (*n* = 535) and validation sample (*n* = 268) are shown in Table 2. There was no statistical imbalance between the two samples. Six percent of patients had PS2 in both samples. There were 252 patients (47%) and 132 patients (49%) with increased LDH level at baseline in the learning and validation samples, respectively, and 224 patients (42%) and 116 patients (43%) with 2 or more metastatic sites at baseline in the learning and validation samples, respectively. Prior adjuvant chemotherapy without oxaliplatin or irinotecan was given in 158 patients (20%).

Table 3. Univariate and multivariate analysis (learning sample)

Variable	Class	Univariate analysis				Multivariate analysis			
		HR	95% CI	<i>p</i>	C	HR	95% CI	<i>p</i>	β
Age	≤65	1.00							
	>65	1.17	0.96–1.42	.101	.52				
Sex	Male	1.00							
	Female	1.10	0.91–1.34	.317	.51				
PS	0	1.00				1.00			
	1	1.78	1.46–2.17	<.001	.60	1.54	1.26–1.90	<.001	.46
No. sites	2	2.38	1.59–3.57	<.001		2.00	1.33–3.02	.001	.75
	1	1.00				1.00			
	>1	1.35	1.11–1.65	.003	.53	1.34	1.09–1.64	.005	.28
Liver involvement	Yes	1.00							
	No	1.06	0.84–1.32	.614	.50				
Primitive tumor	Colon	1.00							
	Rectum	0.95	0.77–1.16	.597	.50				
	Both	1.27	0.47–3.45	.636					
Time to metastasis	Metachronous	1.00				1.00			
	Synchronous	1.28	1.02–1.61	.033	.52	1.09	0.85–1.39	0.508	
Adjuvant CT	Yes	1.00							
	No	0.99	0.78–1.27	.983	.50				
LDH	≤1 × ULN	1.00				1.00			
	>1 × ULN	2.11	1.74–2.57	<.001	.58	1.80	1.45–2.25	<.001	.68
ALP	≤1 × ULN	1.00				1.00			
	>1 × ULN	1.66	1.36–2.02	<.001	.56	1.20	0.96–1.50	.111	
CEA	≤1 × ULN	1.00							
	>1 × ULN	1.28	0.99–1.65	.054	.52				
Harrell's C index						.64			

Abbreviations: ALP, alkaline phosphatase; β , β -regression coefficient; C, Harrell's C index; CEA, carcino-embryonic antigen; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; LDH, lactate dehydrogenase; No. sites, number of metastatic sites; *p*, *p*-value; PS, performance status; ULN, upper limit of normal value.

Follow-up

The median follow-up times for the learning and validation samples were 43.8 months (95% confidence interval [CI], 42.9–47.9) and 46.3 months (95% CI, 43.0–52.4) in the C97-3 trial, 35.3 months (95% CI, 32.1–38.8) and 35.6 months (95% CI, 31.6–43.6) in the OPTIMOX1 trial, and 38.5 months (95% CI, 31.3–46.4) and 39.1 months (95% CI, 32.6–46.7) in the OPTIMOX2 trial, respectively.

Prognostic Factors

Five variables were identified as prognostic factors in the univariate analysis: PS ($p < .001$), LDH ($p < .001$), ALP ($p < .001$), number of sites ($p = .003$), and time to metastasis ($p = .033$). These five variables were introduced in the multivariate analysis. The CEA level at baseline (normal versus increased value) was not statistically significant ($p = .054$) (Table 3, Figure 1).

Independent prognostic factors for decreased overall survival in the multivariate analysis were as follows: abnormal serum LDH level (hazard ratio [HR] = 1.80; 95% CI, 1.45–2.25, $p < .001$), impaired performance status (PS1: HR = 1.54, 95% CI, 1.26–1.90, $p < .001$; and PS2: HR = 2.00, 95% CI, 1.33–3.02, $p = .001$), and >1 metastatic site (HR = 1.34, 95% CI, 1.09–1.64, $p = .005$). The Harrell's C index was 0.64 (Table 3).

Prognostic Model

A new prognostic scoring system was based on the three independent prognostic factors identified in the multivariate analysis: LDH, PS, and the number of metastatic sites. For LDH ≤1 × upper limit of normal (ULN), PS0, and only 1 metastatic site: 0 point each; for PS1 and >1 site: 1 point each; for LDH >1 × ULN and PS2: 2 points each. A score of 0–5 was calculated for each patient. Three risk groups

Figure 1. Overall survival according to independent prognostic factors in learning sample (A–C) and validation sample (D–F). (A): WHO PS (learning sample), (B): serum LDH level (learning sample), (C): number of metastatic sites (learning sample), (D): WHO PS (validation sample), (E): serum LDH level (validation sample), and (F): number of metastatic sites (validation sample). Abbreviations: LDH, lactate dehydrogenase; PS, performance status; WHO, World Health Organization.

were identified in predicting survival: a low-risk group (0 point), an intermediate-risk group (1–3 points), and a high-risk group (4–5 points).

The median OS in the learning sample was 30.1 months (95% CI = 26.7–37.1) in the low-risk group ($n = 118$, 22%), 19.6 months (95% CI = 17.9–21.3) in the intermediate-risk group ($n = 348$, 65%), and 13.1 months (95% CI = 9.4–14.5) in the high-risk group ($n = 69$, 13%). According to low risk, the univariate HR was 1.92 (95% CI = 1.49–2.49) for the intermediate-risk group and 4.51 (95% CI = 3.22–6.33) for the high-risk group. The Harrell's C index for this model was 0.61. Optimism-corrected Harrell

C index was 0.59. Calibration was satisfactory (data not shown).

The median OS in the validation sample was 36.7 months (95% CI, 23.7–58.1) in the low-risk group ($n = 49$, 18%), 19.8 months (95% CI, 17.1–22.1) in the intermediate-risk group ($n = 187$, 70%), and 12.7 months (95% CI, 10.0–19.2) in the high-risk group ($n = 32$, 12%). According to low risk, univariate HR was 2.17 (95% CI, 1.45–3.25) for the intermediate-risk group and 3.24 (95% CI, 1.91–5.48) for the high-risk group. The Harrell's C index for this model was 0.60. Optimism-corrected Harrell C index was 0.56. Calibration was not satisfactory (data not shown).

Table 4. Overall survivals according to scoring system

Sample	High risk		Intermediate risk		Low risk	
	Learning	Validation	Learning	Validation	Learning	Validation
GERCOR model with three variables (PS, no. sites, and LDH)						
<i>n</i> (%)	69 (13)	32 (12)	348 (65)	187 (70)	118 (22)	49 (18)
median OS (mo(s)) [95% CI]	13.1 [9.4–14.5]	12.7 [10.0–19.2]	19.6 [17.9–21.3]	19.8 [17.1–22.1]	30.1 [26.7–37.1]	36.7 [23.7–58.1]
hazard ratio [95% CI]	4.51 [3.22–6.33]	3.24 [1.91–5.48]	1.92 [1.49–2.49]	2.17 [1.45–3.25]	1.00	1.00
Harrell's C index = 0.61 (learning) and 0.60 (validation)						
GERCOR model with two variables (PS and LDH)						
<i>n</i> (%)	128 (24)	72 (27)	223 (42)	112 (42)	184 (34)	84 (31)
median OS (mo(s)) [95% CI]	13.9 [11.1–14.8]	13.2 [11.4–16.5]	19.5 [16.5–21.1]	21.1 [18.1–24.3]	29.8 [26.4–34.7]	26.8 [22.0–36.5]
hazard ratio [95% CI]	3.23 [2.50–4.18]	2.84 [1.97–4.10]	1.92 [1.52–2.43]	1.68 [1.20–2.37]	1.00	1.00
Harrell's C index = 0.64 (learning) and 0.63 (validation)						
Köhne's model with four variables (PS, no. sites, ALP, and WBC)						
<i>n</i> (%)	40 (7)	20 (7)	201 (38)	105 (39)	294 (55)	143 (53)
median OS (mo(s)) [95% CI]	11.1 [8.3–14.5]	9.9 [5.5–14.4]	18.1 [16.3–21.1]	21.4 [18.4–23.6]	22.5 [20.6–25.1]	22.4 [19.5–25.7]
hazard ratio [95% CI]	2.64 [1.86–3.74]	3.73 [2.29–6.08]	1.31 [1.07–1.61]	1.12 [0.84–1.50]	1.00	1.00
Harrell's C index = 0.55 (learning) and 0.55 (validation)						
Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LDH, lactate dehydrogenase; <i>N</i> , number of patients; ND, Not done; no. sites, number of metastatic sites; OS, overall survival; PS, performance status.						

A prognostic score based on the two most important prognostic factors (LDH and PS) was also developed. For LDH $\leq 1 \times$ ULN and PS0: 0 point each; for PS1: 1 point; for LDH $> 1 \times$ ULN and PS2: 2 points each. A score from 0 to 4 was calculated for each patient. Three risk groups for mortality were identified: a low-risk group (0 point), an intermediate-risk group (1–2 points), and a high-risk group (3–4 points) (Table 4, Figures 2 and 3). The median OS in the learning sample was 29.8 months (95% CI, 26.4–34.7) in the low-risk group ($n = 184$, 34%), 19.5 months (95% CI, 16.5–21.1) in the intermediate-risk group ($n = 223$, 42%), and 13.9 months (95% CI, 11.1–14.8) in the high-risk group ($n = 128$, 24%). According to low risk, univariate HR was 1.92 (95% CI, 1.52–2.43) for the intermediate-risk group and 3.23 (95% CI, 2.50–4.18) for the high-risk group. The Harrell's C index for this model was 0.64. Optimism-corrected Harrell C index was 0.63. As shown in supplemental online Figure 1, calibration was satisfactory.

The median OS in the validation sample was 26.9 months (95% CI, 22.0–36.5) in the low-risk group ($n = 84$, 31%), 21.2 months (95% CI, 18.1–24.3) in the intermediate-risk group ($n = 112$, 42%), and 14.0 months (95% CI,

11.4–16.5) in the high-risk group ($n = 72$, 27%). According to low risk, univariate HR was 1.68 (95% CI, 1.20–2.37) for the intermediate-risk group and 2.84 (95% CI, 1.97–4.10) for the high-risk group. The Harrell's C index for this model was 0.63. Optimism-corrected Harrell C index was 0.61. As shown in supplemental online Figure 1, calibration remained satisfactory in the validation sample.

Köhne Model

By applying the Köhne model in the learning and validation samples, median OS was determined to be 22.5 months (95% CI, 20.6–25.1) ($n = 294$, 55%) and 22.4 months (95% CI, 19.5–25.7) ($n = 143$, 53%) in the low-risk group, 18.1 months (95% CI, 16.3–21.1) ($n = 201$, 38%) and 21.4 months (95% CI, 18.4–23.6) ($n = 105$, 39%) in the intermediate-risk group, and 11.1 months (95% CI, 8.3–14.5) ($n = 40$, 7%) and 9.9 months (95% CI, 5.5–14.4) ($n = 20$, 7%) in the high-risk group, respectively.

According to low risk, univariate HR was 1.31 (95% CI, 1.07–1.61) for the intermediate-risk group and 2.64 (95% CI, 1.86–3.74) for the high-risk group in the learning sample. According to low risk, univariate HR was 1.12 (95% CI, 0.84–

Figure 2. Survivals in high-, intermediate-, and low-risk groups in Köhne and GERCOR models (learning and validation samples). (A): Köhne model in learning sample, (B): GERCOR model in learning sample, (C): Köhne model in validation sample, and (D): GERCOR model in validation sample.

		Performance Status			
		PS 0	PS 1	PS 2	
		Points	0	1	2
LDH	≤1xULN	0	0	1	2
	>1xULN	2	2	3	4
0 point		1-2 points		3-4 points	
Low-risk		Intermediate-risk		High-risk	
Learning sample (n = 535)					
N (%)	184 (34)	223 (42)	128 (24)		
Median OS	29.8 months	19.5 months	13.9 months		
[95% CI]	[26.4-34.7]	[16.5-21.1]	[11.1-14.8]		
Validation sample (n = 268)					
N (%)	84 (31)	112 (42)	72 (27)		
Median OS	26.9 months	21.2 months	14.0 months		
[95% CI]	[22.0-36.5]	[18.1-24.3]	[11.4-16.5]		

Figure 3. GERCOR prognostic model. Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; OS, overall survival; PS performance status; ULN, upper limit of normal.

1.50) for the intermediate-risk group and 3.73 (95% CI, 2.29–6.08) for the high-risk group in the validation sample. The Harrell’s C index for this model was 0.55 for both samples

(Table 4). Optimism-corrected Harrell C index was 0.52 in the learning sample and 0.50 in the validation sample. As shown in supplemental online Figure 1, calibration was average.

DISCUSSION

We identified three risk groups for death depending on two baseline parameters, WHO PS and LDH level. Patients with good prognosis had WHO PS0 and normal LDH level at baseline, whereas patients with poor prognosis had WHO PS 1–2 with increased LDH level at baseline. An intermediate-risk group was defined as either WHO PS 0 and increased LDH level or WHO PS 1–2 with normal LDH level at baseline. Median OS in patients with good prognosis was twofold better than patients with poor prognosis in both learning and validation sample and 1.5-fold better than patients with an intermediate prognosis for survival. This simplified prognostic model with only two variables was more discriminate and easier to practice than a model with three variables (WHO PS, LDH level, and number of organs involved). Moreover, the distribution of the patients between the three groups (high-, intermediate-, and low-risk groups) was better in the simplified model than in the model with three variables and in the Köhne model. This model with only two variables will be evaluated in trials using targeted therapies [24].

In this study, LDH was the most important prognostic factor, with a twofold risk for mortality in the case of increased level at baseline. LDH has been previously identified as a prognostic factor in colorectal cancer [4, 5, 9, 11, 25] and other tumor localizations [26–30]. Of note, LDH has also been identified as a potential predictive factor for a vascular endothelial growth factor inhibitor and chemotherapy combination in patients with metastatic colorectal cancer [31].

After LDH, performance status was the strongest prognostic factor associated with OS, with a twofold risk for mortality in case of PS2 compared to patients with PS0 ($HR = 2.00, p < .001$). This result is consistent with a previous study that found that PS2 was prognostic for OS ($HR = 2.18; p < .0001$) [32].

The number of metastatic sites was the third independent prognostic factor identified in this study. As previously shown, a high alkaline phosphatase level at baseline was associated with shorter OS in the univariate analysis [33] but not in the multivariate analysis, like synchronous disease.

CEA level at baseline ($p = .054$) and age ($p = .101$) were not significant in univariate analysis. Sex, liver involvement, primitive tumor localization, and use of prior adjuvant chemotherapy were not prognostic factors in the univariate analysis. An adjuvant therapy without oxaliplatin or irinotecan was given in 20% of the patients. The use of oxaliplatin as adjuvant chemotherapy could influence the therapeutic strategy after relapse, leading to a potential impact on overall survival [34].

There were some drawbacks in the Köhne model, which

was useful in the fluoropyrimidine era. Despite a strong association with survival in the univariate analysis ($p < .0001$), LDH was not introduced in the model, because its value was not available for 72% of the patients. Variations between centers with respect to cutoff values for ALP level were problematic. No information related to discriminant capabilities like Harrell's C index was reported stipulating that recursive partition and amalgamation was the better method to improve discrimination. When this model was applied to our patients treated with more recent chemotherapy regimens, it was not able to separate patients with low- and intermediate-risk for death. Better discrimination was found for our proposed score. Although it could be improved, this model had similar discrimination level (C index 0.64) to validated scores in other settings [35].

Two studies have evaluated the applicability of the Köhne model in patients treated with irinotecan- or oxaliplatin-based first-line chemotherapy. The first was a monocentric and retrospective series of 142 patients [36]. The median survival was 20.0, 15.7, and 6.8 months in the low-risk, intermediate-risk, and high-risk groups, respectively. A larger analysis from a randomized study involving 1,499 patients reported similar results [37]. These two studies have shown that the Köhne model was applicable in this setting. Nevertheless, >50% of the patients were in the low-risk group in the retrospective study, and in the second study, the low-risk and the intermediate-risk groups represented nearly 90% of the whole population.

Better discrimination is needed to improve therapeutic decisions. A combination model of prognostic and predictive factors could lead to a better selection of patients before initiating treatment. A complementary approach could combine different fields in the same model, such as clinicobiological markers, health-related quality of life, [38, 39], molecular markers such as KRAS, BRAF, and PTEN [40–42], gene expression signatures, and detection of circulating tumor cells. However, before identifying new biomarkers, this simple model with only two variables could be used in clinical research for patients' stratification and to adapt the strategy.

Serum LDH level at baseline and WHO PS were the main prognostic factors in predicting survival for patients with previously untreated metastatic colorectal cancer receiving either oxaliplatin-based or irinotecan-based first-line chemotherapy. These two variables should be available in all patients with metastatic colorectal cancer. Three risk groups for death were identified based on these two baseline parameters. This simple prognostic model can be useful for designing future clinical trials to ensure balanced randomization.

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