ORIGINAL ARTICLE

Factors associated with the survival of colorectal cancer in Mexico

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Background/Aims: Colorectal cancer (CRC) is a public health problem. In Mexico, there have been no recent studies conducted on survival in terms of this pathology or on the influence of prognostic factors. The study aims to determine the probability of survival in patients with CRC presence of low levels of schooling and a rural population, adjusted for clinical stage and type of treatment. **Methods:** A retrospective study was conducted in a cohort of 305 patients with CRC treated at State Cancer Center, located in Veracruz-Mexico; the follow-up period of 60 months (2012–2016). The survival probability was calculated using the Kaplan-Meier estimator and the log-rank test with 95% confidence intervals (CIs). Prognostic factors were determined using hazard ratio (HR) multivariate Cox regression analysis. **Results:** Overall survival was 40% at 60 months. Subjects in the age group ≥65 years had a low survival rate of 28% ($P=0.026$) and an advanced clinical stage of 22% ($P<0.001$). Of the patients with bone metastasis, none survived longer than 5 years ($P=0.008$). With respect to the unfavorable prognostic factors identified in the multivariate analysis, a decreased level of schooling was associated with an HR of 7.6 (95% CI, 1.1–54.7), advanced clinical stage was associated with an HR of 2.1 (95% CI, 1.2–4.0), and the presence of metastasis had an HR of 1.8 (95% CI, 1.1–2.9). **Conclusions:** Poor prognostic factors include an advanced clinical stage, the presence of metastasis and a low level of schooling. These findings confirm the importance of screening for early diagnosis, diminishing the barriers to accessing treatment and prospectively monitoring the population. **(Intest Res 2020;18:315-324)**

Key Words: Colorectal neoplasms; Survival; Metastasis; Lymphatic node; Clinical stage

INTRODUCTION

Colorectal cancer (CRC) is a health problem worldwide. CRC is expected to increase due to the growth and aging of the population, as well as the adoption of behaviors and lifestyles that increase the risk of dying.[1,2] In Mexico, where CRC ranks fourth among the most common cancers, most cases are detected after 50 years of age, and the scenario is similar for both sexes. Therefore, the number of new cases and the mortality rates have increased consistently with the growing life expectancy,

which currently presents a global public health problem.[3]

Some sociodemographic characteristics have been studied and have been correlated with survival in several types of cancer, including CRC. Some studies have pointed out that survival is influenced by social inequalities.[4-6] Likewise, the socioeconomic stratum, which affects access to early detection programs and determines the type of health service available.[7] Similarly, lifestyle behaviors in rural area are considered risk factors for this type of cancer.[8] Some countries, such as Brazil, have reported an increase in the incidence of CRC in areas of unequal social stratum and low levels of schooling.[9]

The important advances made in diagnostic and therapeutic techniques, together with prevention programs for early detection of malignancies in the preclinical phase, have contributed to improving the survival ratio.[10,11] Recent studies have

shown that tumors located in the right colon are associated with lower survival compared to those restricted to the left colon, as shown by Loupakis et al.[12]

Long-term disease-free survival following the excision of polyps with metastasis observed due to the development in recent years of advanced surgical techniques. Differences in disease-free survival also depend on the chemotherapy regimen and planned cycles are completed.[13] Polyp resection is indicated when base is between 2 to 2.5 cm.[13] By colonoscopy it is possible to remove up to 70% of the polyps located in the colon and rectum.[14]

Several randomized controlled trials conducted to compare the effectiveness of a series of treatment protocols.[14,15] Age and advanced stage colon cancer are considered predictive of early mortality, as well as disease characteristics such as having more than one positive lymph node, a poorly differentiated tumor and concomitant diseases.[16] Chemoradiation is the treatment of choice in tumors located in the rectum. The survival rate improved in patients with stage III colon cancer.[17]

This study aimed to determine the probability of survival in patients with CRC and to identify the association between survival and low levels of schooling, low socioeconomic status, and location in a rural population, adjusting for the clinical and histologic stages of disease and the type of treatment.

METHODS

1. Study Design and Patients

A retrospective open cohort study was conducted in which all patients diagnosed in the 2010 to 2016 period were included in the State Cancer Center, a tertiary care center, located in Xalapa, Veracruz-Mexico. The maximum and the minimum follow-up period was 60 and 24 months, respectively and the patients were classified as exposed or not exposed according to the level of schooling. The selection criteria were patients with a confirmed diagnosis of CRC who were 18 years or older, of either both sex and who resided in the state of Veracruz. Participants were selected based on information obtained by secondary sources, such as clinical records and information provided by the Department of Social Work. The monitoring included the time interval between the date of diagnosis and the date of the last consultation or the date of death from any cause. For the rest of the cohort, the follow-up time ended on December 31, 2016. This study was approved by the Research Ethics Committee of State Cancer Center, Secretary of Health of the State of Veracruz (approval No. SEIC-006-16). This study

is a retrospective study using medical record review and so informed consent was waived.

2. Variables

The main response variable was the survival of patients with CRC defined as the time between the confirmation of the diagnosis of CRC and the death of the patient. The death was verified through the death certificate provided by the social work coordination and by the records of the Epidemiological System and Death Statistics.

The predictor variables were a low level of schooling, defined as "less or equal" level of secondary schooling; socioeconomic status, defined as the number that indicates the social and economic position in which the patient's family is located; and the rural population, defined as the population with less than 2,500 inhabitants.

Other covariables recorded were tumor size, histological type and clinical stage of disease using the criteria of the American Joint Commission on Cancer and the World Health Organization (WHO). Sociodemographic variables that were also included were the type of diagnosis and treatment, the date of the last contact and the date of death, as well as the presence of associated pathologies. The criteria for socioeconomic classification were the following variables with their respective weight: family income (55%), job (10%), family expenses (10%), housing (20%), and family health (5%).

3. Scales and Questionnaires

Experts from the study's headquarters hospital and the Instituto Nacional de Oncología, located in Havana, Cuba, validated the collection card. The following information collected through the clinical file: diagnosis of CRC (histological tissue and colonoscopy). The date and cause of death were obtained from the death certificate.

The size of the sample was calculated from the results of a cohort study by Lejeune et al.,[18] where it was found that the survival of the subjects with a low level of education was 57.1% (HR, 0.73; 95 CI, 0.57–0.94). With the information mentioned above and considering a confidence level of 95% and a minimum power of 80%, the sample size calculated was 104 patients.

4. Statistical Analysis

Descriptive statistics were used for sociodemographic, clinical, and histological characteristics and those related to the treatment of the studied cohort. The survival analysis was cal-

culated with the Kaplan-Meier method. Survival probabilities were compared for each possible prognostic factor using the log-rank test. Subsequently, the prognostic factors adjusted for possible confounders in a multivariate analysis using Cox regression, where the dependent variable was age, and the covariates were clinical stage, histological type, level of schooling, place of residence. The HRs and their respective 95% CIs were calculated. Losses during the monitoring were considered censored data and were contributed to the sum of the total person-time. The statistical package IBM SPSS statistics software (IBM Corp., Armonk, NY, USA), for Windows version 23.0, was used for analysis.

RESULTS

Of the 323 patients initially considered, the following were excluded: 5 resided in another geographical area, 8 had recurrent CRC, and 5 had another type of cancer added to the primary malignancy. In total, the study sample consisted of 305 patients, mostly men, with a minimum and maximum age of 18 and 96 years, respectively. The population from rural areas predominated, had an educational level equal to or lower than the basic level, had mostly paid employment, and almost the entire population was registered at a low socioeconomic status (Table 1).

The methods used to diagnose suspicion of CRC were, 66% colonoscopy, 20.5% imaging tests and 13.5% surgery. The frequency tumors stages were II 29%, III 30.6%, and IV 33.3%, principally located in the rectum and were greater than 5 centimeters. The liver was the organ most frequently affected by distant metastasis, and adenocarcinoma was the most common histological type (Table 2).

The most frequent symptoms were colic (49.2%), combined with weight loss and rectal bleeding (43.6%), among other symptoms. The most frequent types of comorbidities were arterial hypertension (34.8%) and diabetes mellitus (28.3%). The most frequent treatment undergone was a combination of surgery with chemotherapy, as well as chemotherapy with oxaliplatin (Table 2).

1. Survival Ratio
The overall survival ratio for the cohort at 60 months of monitoring was 40%. A greater statistically significant survival was observed in patients >65 years of age ($P=0.03$) who had a high level of education ($P=0.02$) (Table 3). Those patients with an early clinical stage ($P<0.001$) and without metastasis ($P<0.001$)

Table 1. Sociodemographic and Clinical Characteristics of the Cohort Participants (n = 305)

Variable	No. of patients (%)
Age (yr)	
< 65	208 (68.2)
≥ 65	97 (31.8)
Sex	
Male	178 (58.4)
Female	127 (41.6)
Place of origin	
Rural	196 (64.3)
Urban	109 (35.7)
Occupation	
Worker	163 (53.4)
Housework	116 (38.1)
Unemployed	26 (8.5)
Clinical stage[a]	
Local	132 (51.2)
Regional	40 (15.5)
Distant	86 (33.3)
Level of education	
Illiterate	132 (43.3)
Primary/secondary education	152 (49.8)
High school/university	21 (6.9)
Location of the tumor	
Blind	40 (13.1)
Ascending+descending colon	81 (26.6)
Transverse colon	22 (7.2)
Sigmoid	52 (17.0)
Straight	110 (36.1)
Tumor size (cm)	
≤ 5	97 (34.8)
> 5	182 (65.2)
Metastatic lymph nodes	
No	250 (82.0)
Yes	55 (18.0)
Location of metastasis	
Liver	41 (41.4)
Lung	15 (15.2)
Bone	5 (5.0)
Others	38 (38.4)

[a]Unclassified = 47 patients.

had a high probability of survival (Table 4). When evaluating the types of treatment, when a combination included surgical treatment, survival was 41% ($P=0.012$) (Fig. 1).

Table 2. Sociodemographic and Clinical Characteristics of the Cohort Participants

Variable	Education		P–value[a]
	Low (n = 284)	High (n = 21)	
Age (yr)			0.070
< 65	190 (66.9)	18 (87.5)	
≥ 65	94 (33.1)	3 (14.3)	
Sex			0.170
Male	167 (58.8)	11 (52.4)	
Female	117 (41.2)	10 (47.6)	
Place of origin			0.002
Rural	189 (66.5)	7 (33.3)	
Urban	95 (33.5)	14 (66.7)	
Occupation			0.730
Worker	151 (49.5)	12 (57.1)	
Unemployed	55 (50.5)	9 (42.9)	
Clinical stage			0.960
Early	87 (30.6)	6 (28.6)	
Advanced	153 (53.9)	12 (57.5)	
Unclassified	44 (15.5)	3 (14.3)	
Location of the tumor			0.230
Blind	38 (13.5)	2 (9.5)	
Ascending+descending colon	77 (27.3)	4 (19.0)	
Transverse colon	17 (7.4)	4 (19.0)	
Sigmoid	47 (16.7)	4 (19.0)	
Straight	103 (36.5)	7 (33.3)	
Tumor size (cm)			0.190
2–5	93 (35.8)	4 (21.1)	
> 5	167 (64.2)	15 (78.9)	
Metastatic lymph nodes			< 0.001
No	239 (84.2)	11 (52.4)	
Yes	45 (15.8)	10 (47.6)	
Location of metastasis			0.030
Liver	40 (41.7)	1 (33.3)	
Lung	13 (13.5)	2 (66.7)	
Others	43 (44.8)	0	
Type of treatment (n = 261)			0.170
Surgery	18 (18.2)	1 (5.0)	
Chemotherapy	23 (23.2)	5 (25.0)	
Radiotherapy	1 (1.0)	1 (5.0)	
Surgery and chemotherapy	37 (37.4)	10 (50.0)	
Surgery and radiotherapy	3 (3.0)	1 (5.0)	
Chemotherapy and radiotherapy	7 (7.1)	1 (5.0)	
Surgery+chemotherapy+radiotherapy	10 (10.1)	1 (5.0)	

(*Continued to the next page*)

Table 2. Continued

Variable	Education		P–value[a]
	Low (n = 284)	High (n = 21)	
Type of chemotherapy (n = 182)			0.590
Neoadjuvant	61 (33.5)	5 (27.8)	
Adjuvant	121 (66.5)	13 (72.2)	
Scheme of chemotherapy (n = 163)			0.960
Oxaliplatin	59 (39.6)	5 (35.7)	
XELOX	37 (24.8)	4 (28.6)	
FOLFOX	15 (10.1)	2 (14.3)	
5 FU	20 (13.4)	16 (14.3)	
Others	18 (12.1)	1 (7.1)	

[a]Comparison of proportions using chi square (Fisher exact test was used when necessary).
XELOX, capecitabine (Xeloda) and oxaliplatin; 5 FU, 5-fluorouracil; FOLFOX, oxaliplatin, 5-FU, and leucovorin.

Table 3. Survival According to Sociodemographic Characteristics (n = 305)

Variable	No. of subjects	2-Year survival rate (%)[a]	5-Year survival rate (%)[a]	P–value[b]
Age (yr)				0.03
< 65	208	68	48	
≥ 65	97	56	28	
Sex				0.62
Male	178	67	44	
Female	127	61	38	
With partner or spouse				0.89
Yes	111	65	45	
Do not	194	63	33	
Provenance zone				0.85
Urban	109	65	43	
Rural	196	63	39	
Level of education				0.02
Low	284	62	37	
High	21	86	86[c]	
Employment situation				0.34
Worker	163	70	42	
Unemployed	142	58	36	
Socioeconomic level				NA[d]
Low	295	63	38	
High	10	99.9	99.9	

[a]Kaplan-Meier method.
[b]Log-rank test.
[c]Maximum survival of 58 months.
[d]NA: not applicable because some of the categories of the variables showed an expected value less than 5.

2. Prognostic Factors

After adjusting for age (< 65 years and ≥ 65 years), the following variables showed a significant association with survival: low level of schooling, tumors in an advanced clinical stage and the presence of metastasis, all of which increased the risk of dying due to poor prognostic factors (Table 5).

DISCUSSION

There is a wide variation in survival between different geographical areas; due to differences in exposure to risk factors for CRC, access to cancer diagnosis and type of treatment. As shown in our results, the 5-year global survival was very low, similar to that reported in other Latin American countries, such as Chile and Colombia.[19,20]

Similarly, these inconsistencies in survival attributed to the inequalities in socioeconomic status and the geographic area of origin.[9] Even the low level of schooling related to an increased risk of CRC.[21] A low 37% survival in the population was associated with a low level of education, which, in the multivariate analysis, was a poor prognostic factor (HR, 7.46; 95% CI, 1.02–54.7) in our cohort study. Similar results were reported by Cavalli-Björkman et al.[22] In contrast, a recent study suggested that a high level of schooling was a protective factor against CRC (HR, 0.61; 95% CI, 0.39–0.92), compared to illiterate patients.[23] Additionally, the education level was associated with the histological type of CRC and with the age of the subject in that, the young people developed aggressive tumors according to the histological differentiation.[24,25]

The clinical stage is still considered an element that can guide

Table 4. Survival According to Tumor Characteristics and Treatment

Variable	No.	2-Year survival rate (%)[a]	5-Year survival rate (%)[a]	P-value[b]
Clinical stage				< 0.001
Early	93	82	68	
Advanced	165	56	22	
Tumor location				0.700
Descendent colon	21	75	75	
Blind	40	75	55[c]	
Transverse colon	21	63	50[d]	
Rectum	110	61	46	
Ascendant colon	60	60	33	
Sigmoid colon	51	84	19	
Tumor size (cm)				0.700
< 2	11	60	45[e]	
2–5	86	66	49	
> 5	182	65	39	
Metastatic lymph node				0.110
0	249	60	42	
1–3	29	68	34[f]	
≥ 4	26	88	0	
Presence metastasis				< 0.001
Negative	204	71	57	
Positive	101	47	0	
Distant metastases				0.008
Lung	15	74	48[g]	
Liver	41	24	0[h]	
Lung and liver	9	0	0	
Bone	5	53	0	
Others	29	57	0	
Histologic grade				0.170
Grade 1	195	24	41	
Grade 2	68	70	39	
Grade 3	32	50	37[i]	
Type of chemotherapy				0.150
Adjuvant	61	61	34	
Neoadjuvant	121	70	40	
Scheme of chemotherapy				0.320
5 FU	22	73	63	
Capecitabine	16	57	57	
Oxaliplatin	64	70	43	
FOLFOX	17	62	31	
XELOX	41	68	0	
Others	3	50	0	

[a]Kaplan-Meier method.
[b]Log-rank test.
[c]Maximum survival of 56 months.
[d]Maximum survival of 49 months.
[e]Maximum survival of 42 months.
[f]Maximum survival of 58 months.
[g]Maximum survival of 55 months.
[h]Maximum survival of 56 months.
[i]Maximum survival of 56 months.
5 FU, 5-fluorouracil; FOLFOX, oxaliplatin, 5-FU, and leucovorin; XELOX, capecitabine (Xeloda) and oxaliplatin.

therapeutic treatment and constitutes a prognostic factor in patients.[26] In the study in general, more than 60% of tumors diagnosed in advanced stages, implied a lower survival and a higher risk of dying from CRC. In recent reports, the International Agency for Research on Cancer showed a high incidence of advanced stages of CRC not only in developing countries but also in developed countries.[1] This is the case in Mexico and specifically for the cohort under study with a high degree of marginalization. In agreement, other studies conducted in populations of low socioeconomic status or located in remote areas showed a high incidence of advanced stage disease, revealing the lack of early detection programs and, in some contexts, poorer standards of care and difficulty in accessing screening tests.[1,9,23,26]

In addition, the same effect observed in our results of advanced stage disease: a very low survival of 22%, unlike the rate of survival in the early stages (68%), similarity with what has been reported for this type of cancer.[27,28] These data indicate CRC diagnosis at late stage, reducing the probability of survival, which suggests the need to increase efforts for detection in early stages.

In the multivariate analysis (Table 5), stages III and IV emphasized as poor prognostic factors with an HR of 2.24 (1.15–4.36), which coincides with the findings by Sharkas et al.[27] who reported, when subdividing the tumor into regional and distant metastasis (HR, 1.8; 95% CI, 1.6–3.7; HR, 4.5; 95% CI, 3.7–5.1, respectively).

Our results, consistent with the current literature, have shown that the presence of metastasis shown to be an important predictor of recurrence and poor survival and was the main cause of mortality in patients with CRC.[29] We observed that a significant number of these patients experienced early metastasis in the liver, followed by metastasis to the bone and the lung. Due to the location, size, and extent of metastasis, no patient survived after 5 years. The prognosis and clinical characteristics of bone metastasis in CRC poorly studied due to their low incidence and insufficient research.[30,31]

The main factor linked to improved survival in CRC, according to the literature, is the progress that made with adjuvant treatments after surgery.[32,33] While undergoing some surgical procedures they showed a better effect on survival (47%) than not undergoing surgery (27%) (P = 0.002) (Fig. 1E). However, 5-fluorouracil monotherapy was the treatment with the highest survival rates. Surgery in this type of neoplasm is very invasive, and the older the patient, the greater the risk of developing complications, which is also associated with the patient's living con-
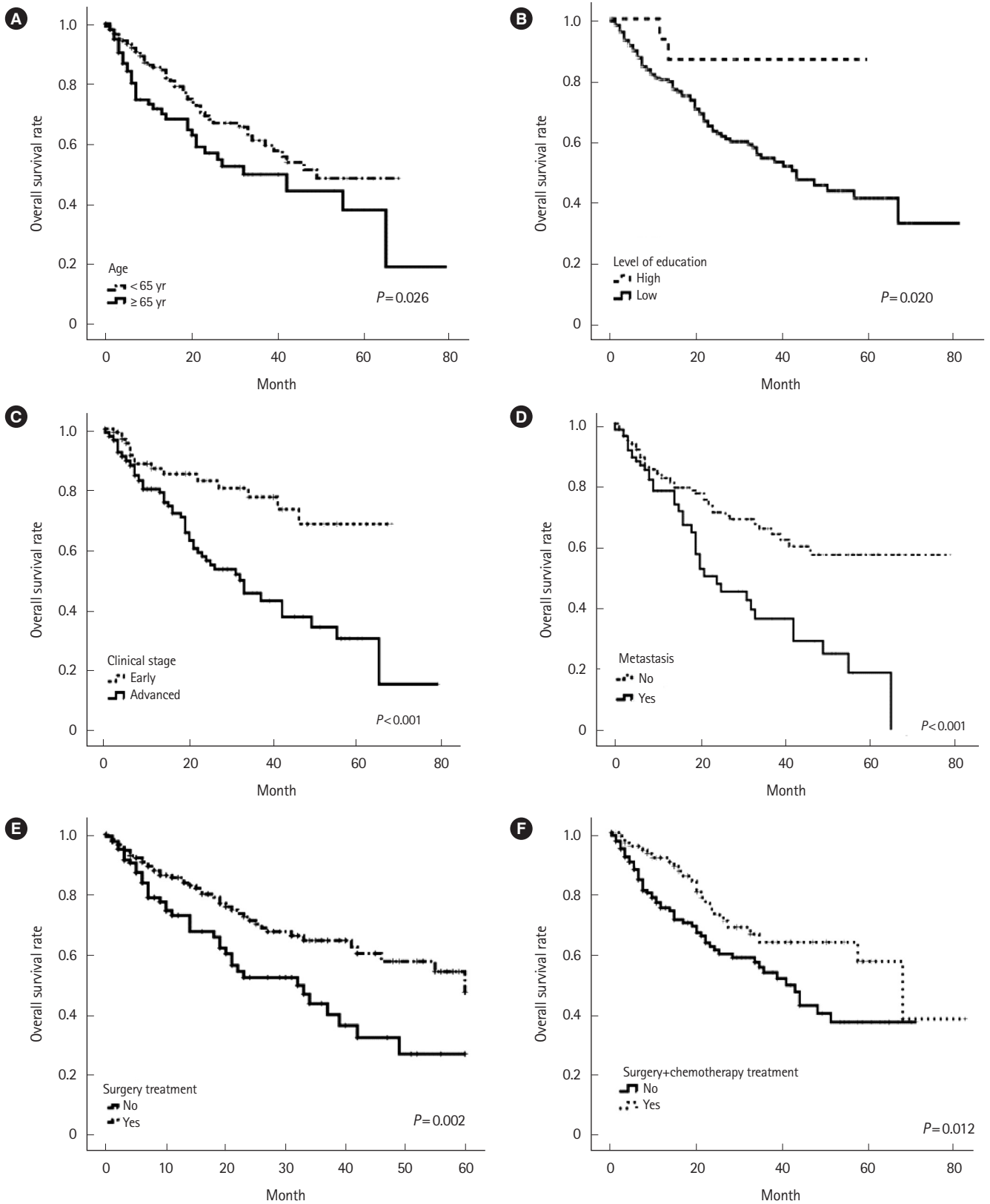
Fig. 1. Kaplan-Meier curves of overall survival colorectal cancer. (A) Age, (B) level of education, (C) clinical stage, (D) metastatic, (E) treatment with surgery, and (F) treatment with chemotherapy.

Table 5. Multivariate Analysis in Variables of Factors Associated with the Survival of Colorectal Cancer

Covariable	Unadjusted model HR (95% CI)	P-value	Adjusted model HR (95% CI)	P-value
Age (yr)				
< 65	Reference		Reference	
≥ 65	1.4 (0.8–2.2)	0.20	-	
Schooling				
High	Reference		Reference	
Low	7.3 (1.0–53.3)	0.05	7.6 (1.1–54.7)	0.04
Origin				
Urban	Reference		Reference	
Rural	0.8 (0.5–1.2)	0.20	-	0.19
Clinical stage				
Early	Reference		Reference	
Advanced	2.1 (1.1–4.0)	0.03	2.1 (1.2–4.0)	0.02
Metastasis				
Absence	Reference		Reference	
Presence	1.7 (1.02–2.9)	0.04	1.8 (1.1–2.9)	0.03
Treatment 1				
Without surgery	Reference		Reference	
With surgery	0.9 (0.5–1.7)	0.81	-	0.26
Treatment 2				
With surgery chemotherapy	Reference		Reference	
Without surgery chemotherapy	0.7 (0.4–1.4)	0.29	-	0.09

ditions.

In contrast, we identified that the combination of surgical treatment and chemotherapy showed the best survival at 38%. However, another study showed a survival of only 58.3% with surgery, and survival in patients who received adjuvant chemotherapy increased to 83.4%.[33] Analogous results reported for localized tumors that were operated on and treated with 5FU postoperatively, and they showed a great benefit in stage III.[32] The studies described previously conducted in developed countries, such as Japan and the United States, where prevention programs implemented and living conditions differ from those of our study cohort.[33]

CRC represents a large global burden that predicted to increase due to the growth and aging of the population because of the adoption of behaviors and lifestyles that increase the risk of developing CRC. By recognizing this growing problem in Mexico and implementing consistent monitoring (pre- and postsurgical), the poor survival associated with CRC and the rate of recurrence could help spur efforts to optimize manage-

ment by increasing the availability of effective access to timely detection. Intensifying educational protocols in the management and control of CRC risk factors and disseminating information that will trigger a social response in accordance with the available conditions and resources.

Finally, the predictor with the highest association to low survival was "less or equal" to the level of secondary schooling (HR, 7.6; 95% CI, 1.1–54.7), which was independent of other covariates, such as occupation or profession and economic income; the latter was not analyzed since all patients reported the lowest economic level. However, other indicators were included that gave a good approximation of the socioeconomic status.

Implementing a screening program and developing additional strategies based on the population at risk of CRC would reduce the gap between the survival of patients with high and low schooling, as well as decrease the incidence of CRC in the coming years. In addition, these strategies could reduce the degree of disease progression in preclinical and clinical pa-

tients, thus accelerating treatment and reflecting favorable changes in survival.

The strengths of the present study were the inclusion of the sample size, the collection of standardized data and a limited loss during follow-up. Information bias was reduced by corroborating all clinical records. An approved criterion when making multidisciplinary decisions. The main limitations of this study include the retrospective nature of this study and the restrictions inherent to the quality of the information in the clinical records that belong to the heterogeneous population and the use of different diagnostic methods. Our study had another limitation: it included a percentage of unclassified patients from a public institution.

In conclusion, regarding the variables that influenced survival, the presence of metastasis, advanced disease and low education were determined to be predictive in more than half of the cases studied that were diagnosed in advanced stages (III-IV) and had a lower overall survival. Possible explanations include late diagnosis, barriers to timely access to care and effective treatment and underlying comorbidities.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Conceptualization: Alvarez-Bañuelos MT, Quezada-Gutiérrez C, Guzmán-García RE. Methodology: Alvarez-Bañuelos MT, Quezada-Gutiérrez C, Morales-Romero J. Validation: Alvarez-Bañuelos MT, Sampieri CL, Monte-Villaseñor E. Formal analysis: Morales-Romero J, Quezada-Gutiérrez C. Investigation: Quezada-Gutiérrez C, Alvarez-Bañuelos MT. Writing-original draft preparation: Quezada-Gutiérrez C, Alvarez-Bañuelos MT. Writing-review and editing: Sampieri CL, Morales-Romero J, Guzmán-García RE. Supervision: Alvarez-Bañuelos MT, Morales-Romero J, Monte-Villaseñor E. Approval of final manuscript: all authors.

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