ORIGINAL ARTICLE

Convined clinical prognostic model in colorectal cancer

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Abstract

Current staging systems in patients with colorectal cancer (CRC) utilize relatively few patient characteristics in comparison to the breadth of information available. The objective of our study is to analyze the heterogeneous set of variables that may influence mortality and recurrence independently in patients with CCR, and prepare a predictive model of survival and recurrence. Data from 288 patients who had undergone scheduled surgery for stage I-III cancer of the colon and upper rectum were used to construct Cox models for DFS and overall CSS at five years. We have jointly examined clinical variables, serological markers and histological variables with the aim of identifying new prognostic factors. Internal and external validation was carried out on each of the nomograms obtained. Perineural invasion; high platelet-lymphocyte ratio (PLR) and the pN stage were the variables that emerged as an independent risk factor of recurrence. The variables related independently to overall CSS were the presence of blood in stools, high PLR and nodal involvement. We have created a predictive model of recurrence and mortality at 5 years with data that is easily available (clinical, analytical and histological variables) which can help personalize the treatment and follow-up of patients with CRC. We also conducted an adequate internal and external validation.

Graphical abstract
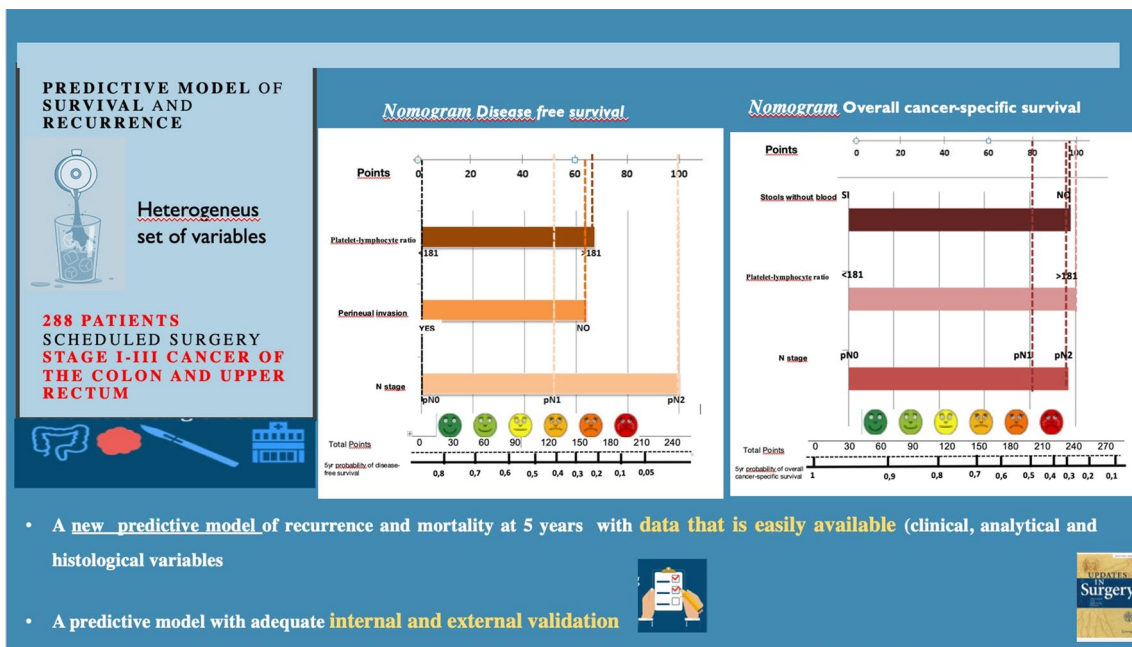
Keywords Colorectal cancer · Prognostic factors · Nomogram

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Introduction

Colorectal cancer (CRC) is the most frequent neoplasia of the digestive tract and represents the fourth cancer-related cause of death in developed countries [1].

The predictive factors of survival and relapse for patients with CRC are multiple and heterogeneous [2]. Current staging systems in patients with CRC are based on logistic regression models, and in general utilize relatively few patient characteristics in comparison to the breadth of information available. Moreover, the clinical relevance and quality of the predictive models of mortality and recurrence in patients with CRC have not been evaluated correctly in the literature [3].

The AJCC's TNM staging system of prognostic classification is the most widely used predictive system. However, this system does not consider certain characteristics of the patient or the tumor itself which have nevertheless shown correlation with recurrence or survival [4].

Furthermore, there are very few nomograms that incorporate newly described prognostic variables like inflammatory markers, molecular markers or other factors or situations whose role in the prognosis is not fully established, such as the patient's clinical situation at the time of diagnosis, for example [5].

The objective of our study is to analyze the heterogeneous set of variables (clinical, analytical and histological) that may influence mortality and recurrence independently in patients with stage I–III cancer of the colon and upper rectum, and prepare a predictive model of survival and recurrence which will be validated according to the recommended statistical methodology [7].

Materials and methods

Patients (patients' cohort)

Information was gathered from 288 patients who had undergone scheduled surgery for stage I-III cancer of the colon and upper rectum at the Badajoz University Hospital over the period from January 2011 to August 2016.

Excluded were patients who did not undergo a complete resection of the tumor, those with distant metastases, and those who underwent neoadjuvant treatment prior to surgery. Patients given emergency surgery, those with macroscopic tumor perforation and those with a history of abdominal tumor over the ten years prior to surgery were similarly not included.

This study was approved by our hospital's Ethics Committee.

Clinical-pathological variables and laboratory data

Data were gathered from each patient retrospectively based on the clinical history. The laboratory data were taken from the blood sample extracted prior to the intervention.

Follow-up

The follow-up of the patients included in the study was based on: physical examination, monitoring of the Carcinoembryonic Antigen (CEA) every 3–6 months during the first two years and every 6 months for up to 5 years thereafter, thoracic, abdominal and pelvic computed tomography (CT) every 3–6 months during the first two years and every 6–12 months up to the fifth year of follow-up; colonoscopy in the first year of follow-up and subsequently every 2–5 years.

Adjuvant chemotherapy was indicated according to the latest recommendations of the National Comprehensive Cancer Network (NCCN) [6].

Disease-free survival (DFS) was defined as the time that passed between the primary radical surgical treatment of the neoplasia and the diagnosis of relapse or the date of the last check-up without relapse in follow-up. Overall cancer-specific survival (CSS) begins with the surgical treatment and ends with the demise of the patient caused by the cancer or on the last date on which it is determined that the patient is alive. Patients who die due to other causes are considered censored.

Statistical analysis

The optimal cutoff values of the continuous analytical variables were calculated using ROC curves.

The numerical analytical variables that showed an adequate AUC were studied as categorical variables and the rest as numerical variables.

The predictive model was created using Cox proportional hazards regression.

Creation of the predictive models

In the initial phase, we performed a univariate statistical analysis in which we separately analyzed each of the variables included in the study and their possible relationship in the recurrence and mortality due to cancer. In the second phase, the variables associated with the oncological results with which a p-value of below 0.1 was obtained in the first phase were included in the multivariate analysis. Using the "backwards steps" method, the predictive models were adjusted for both cases, cancer-specific mortality and tumor recurrence.

Analysis for validation of the adjusted models

Internal and external validation was carried out on each of the nomograms obtained. For the internal validation of the models bootstrapping was used. The external validation of each of the nomograms created was performed based on the information provided by an external sample of patients (from other nearby health areas) with similar characteristics to the patients in our study sample. To evaluate the calibration of the models, a comparison was made of the recurrence and survival curves at 5 years provided by the model with the corresponding curves observed. The discriminative capacity of the models was valued using Harrell's C concordance statistic [8].

Results

Over the study period (January 2011–August 2016) 288 patients with stage I–III cancer of the colon and upper rectum met the inclusion criteria and were included in our study. A detailed summary of the demographic characteristics, personal background of the patients studied, data at the time of diagnosis and anatomopathological characteristics of the tumors is provided in Tables 1 and 2 (Annex I).

To assess the precision of the serological markers, we calculated the area under the ROC curve for each of them, and after this study only the neutrophil-to-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) emerged as suitable prognostic biomarkers. For this reason, these two serological markers were categorized according to their optimal cutoff point and the others were analyzed as numerical variables. The area under curve (AUC) obtained for the variables NLR and PLR were 0.62 and 0.64 respectively (Fig. 1, Annex I). The optimal cutoff point for NLR was 4.4 and for PLR it was 181; with a high specificity and reasonable sensitivity, in accordance with our research objectives (0.85 and 0.25 for NLR and 0.7 and 0.52 for PLR, respectively).

The average follow-up time of the patients included in the study was 32.7 months (0.1–77 months), with a recurrence rate of 15.6% (45 patients) during the follow-up period, and the average recurrence time was 19.5 months (1.3–68.8 months). The DFS at 5 years was 75%. The overall CSS probability of the patients diagnosed with CRC in our study was 91.6% (at 3 years) and 83.8% (at 5 years).

Tables 1 and 2 present the results obtained after performing the corresponding univariate and multivariate statistical analyses to determine the variables related to the recurrence event (Table 1) and mortality (Table 2).

After performing the multivariate analysis, the variables that emerged as an independent risk factor of recurrence were the existence of perineural invasion ($p = 0.007$, HR = 2.47, IC 95%1.8–4.75); high PLR ($p = 0.004$; HR = 2.58,

Table 1 Univariate and multivariate analyses DFS

	Univariante analysis			Multivariante analysis	
	No (%)	p	HR	(95%CI)	p
Garder (Male)	178 (61.8)	0.65			
Age (> 70 years)	163 (56.6)	0.27			
Abdominal pain	44 (15.3)	0.18			
Blood in stools	78 (27.1)	0.14			
Anemia	116 (40.3)	0.16			
Alteration in GI function	64 (22.2)	0.15			
Incidental diagnosis	35 (12.1)	0.99			
Cardiovascula risk factors	221 (76.7)	0.48			
Respiratory disease	54 (18.7)	0.5			
Immunotherapy	11 (3.8)	0.59			
ASA (III/IV)	107 (78.8)	0.54			
Tumor localization(right)	134 (46,5)	0.94			
Endoprosthesis	12(4,16)	0.28			
Synchronous	18 (6.2)	0.24			
T stage (T3–T4)	236 (75%)	0.02	3.32	0.91–12.16	0.19
N stage					**0.002**
N0	187 (64.9)	0.000	1		
N1	72 (25.0)		2.14	1.4–4.50	
N2	29 (10.1)		4.10	1.87–9.01	
No. Lymph nodes	288	0.38			
Differentiation (Poor)	31 (10.8)	0.68			
Venous Invasion	65 (22.6)	0.006	1.18	0.50–2.77	0.72
Lymph invasion	68 (23.6)	0.010	0.41	0.07–2.56	0.34
Perineural invasion	56 (19.4)	0.003	2.47	1.8–4.75	**0.007**
Adjuvant chemo-therapy	139 (48.3)	0.01	1.35	0.61–2.98	0.45
Anastomotic leak	24 (8.3)	0.32			
Clavien-Dindo (III–IV)	38 (31.7)	0.63			
Preoperative anemia	186 (64.6)	0.24			
Preoperative pro-teins	276 (95.83)	0.44			
CEA (ng/mL)	175 (60.76)	0.95			
NLR[a]-high (> 4.4)	44 (15.3)	0.002	1.482	0.63–3.50	0.37
LMR[b] (mean)	278	0.25			
PLR[c]-high (> 181)	92 (31.9)	0.000	2.58	1.36–4.89	**0.004**

Significant results are highlighted in bold

[a]Neutrophil-to-lymphocyte ratio

[b]Lymphocyte-to-monocyte ratio

[c]Platelet-to-lymphocyte ratio

Table 2 Univariate and multivariate analyses CSS

	Univariante analysis		Multivariante analysis		
	No (%)	p	HR	(95%CI)	p
Garder (Male)	178 (61.8)	0.5			
Age (> 70 years)	163 (56.6)	0.7			
Abdominal pain	44 (15.3)	0.73			
Blood in stools	78 (27.1)	0.02	0.24	0.05–1.04	**0.06**
Anemia	116 (40.3)	0.47			
Alteration in GI function	64 (22.2)	0.44			
Incidental diagnosis	35 (12.1)	0.39			
Cardiovascular risk factors	221 (76.7)	0.80			
Respiratory disease	54 (18.7)	0.81			
Immunotherapy	11 (3.8)	0.69			
ASA (III/IV)	107 (78.8)	0.68			
Tumor localization(right)	134 (46.5)	0.20			
Endoprosthesis	12(4.16)	0.03			
Synchronous	18 (6.2)	0.43			
T stage (T3–T4)	236 (75%)	0.18			
N stage					**0.02**
N0	187 (64.9)	0.000	1		
N1	72 (25.0)		3.18	1.21–8.41	
N2	29 (10.1)		4.11	1.22–13.80	
No. Lymph nodes	288	0.46			
Differentiation (Poor)	31 (10.8)	0.49			
Venous Invasion	65 (22.6)	0.02	2.19	0.32–14.69	0.41
Lymph invasion	68 (23.6)	0.03	0.842	0.26–2.63	0.76
Perineural invasion	56 (19.4)	0.05	1.87	0.73–4.97	0.21
Adjuvant chemotherapy	139 (48.3)	0.05	0.84	0.24–3.02	0.76
Anastomotic leak	24 (8.3)	0.19			
Clavien-Dindo (III–IV)	38 (31.7)	0.82			
Preoperative anemia	186 (64.6)	0.03	1,66	0.58–4.75	0.44
Preoperative proteins	186 (64.6)	0.34			
CEA (ng/mL)	175	0.82			
NLR[a]-high (> 4.4)	44 (15.3)	0.05	0.73	0. 25–2.47	0.6
LMR[b] (mean)	278	0.89			
PLR[c]-high (> 181)	92 (31.9)	0.007	4.23	1.71–10.49	**0.002**

Significant results are highlighted in bold

[a]Neutrofil-to-lymphocite ratio

[b]Lymphocite-to-monocyte ratio
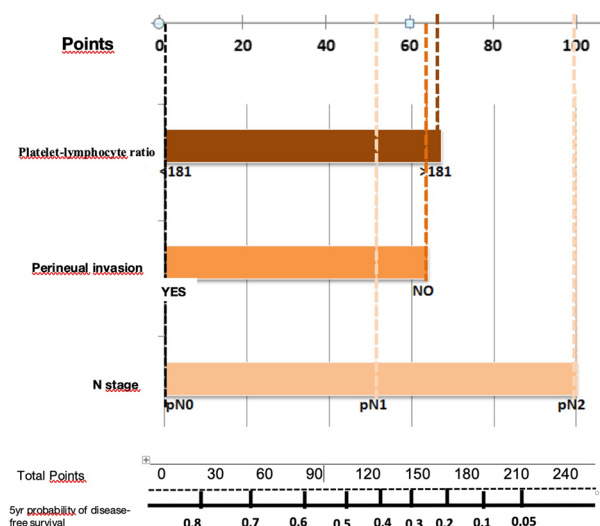
[c]Platelet-to-lymphocite ratio

Fig. 1 Predictive nomograms of disease-free survival of patients with colorectal cancer at 5 years. Nomograms can be deciphered by adding the points assigned to each included variable shown at the top of the scale. The total points generate the predicted 5 year probability of recurrence/metastasis, as indicated on the lowest scale

1,71–10); and nodal involvement ($p = 0.02$; HR 4.11 for N2; IC 95% 1.22–13.8).

Based on the results of multivariate analysis by the Cox regression model, we have prepared two predictive nomograms for DFS and overall CSS at 5 years (Figs. 1 and 2). Using the HR calculated in the multivariate analysis as the specific weight of each variable, we created a nomogram
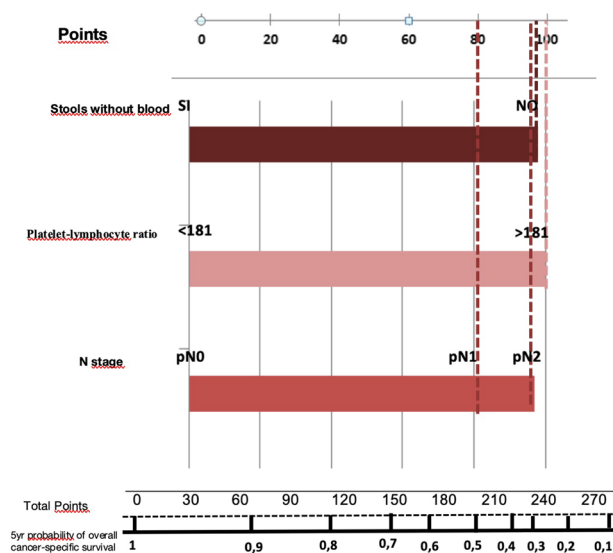

Fig. 2 Predictive nomograms of overall cancer-specific survival of patients with colorectal cancer at 5 years. Nomograms can be deciphered by adding the points assigned to each included variable shown at the top of the scale. The total points generate the predicted 5 year probability of death as indicated on the lowest scale

IC95% 1.36–4.89); and the pN stage (with a maximum, in pN2, of HR 4.10; IC95% 1.87–9.01; $p = 0.007$).

The variables related independently to overall CSS were the presence of blood in stools ($p < 0.06$; HR 0.24, IC95% 0.05–1.04); high PLR ($p = 0.002$, HR = 4.23, IC95%

with which one can simply and graphically calculate the individual probability of DFS and overall CSS at five years for each patient.

To achieve greater reliability in these two "new" variables, the final adjusted models for DFS and overall CSS were validated internally using a bootstrapping (resampling) method. A total of 10,000 resamples were taken from the database, with each one of the models. The HRs obtained were similar to those determined with our group of study patients.

External validation was performed through a comparative study of the predictions in an external group of patients from other hospitals in our Autonomous Community, all of them patients with similar characteristics to those of our study sample (Table 3).

The corresponding Harrell's C concordance indices obtained were 0.82 and 0.83 for the prediction of DFS and overall CSS at 5 years, respectively. Figure 3 represents the calibration curves of each of the nomograms.

Table 3 …

	Patients' cohort (288)	External group of patients (98)	p
Age (years)	71	67	0.06
Gender (Male/Female)	178/109	53/25	0.33
Cardiovascular risk	74.4%	67.3%	0.06
Tumor location	53.3%	58.8%	0.47
Procedure (Right hemicolectomy)	34.4%	43.2%	0.56
Stage (III)	35.2%	41.2%	0.54
Complications	41.8%	45%	0.19

Discussion

This study satisfies the need to know the prognostic factors that will influence the evolution of patients with cancer of the colon and upper rectum who undergo curative surgery in a tertiary hospital endowed with a surgery unit specializing in CRC. One clear objective for us from the outset was that of working with a homogeneous sample, as a result of which we decided to exclude mid and lower-rectal tumors as they are anatomically different from the rest and characterized by a different clinical behavior and therapeutic management [5]. We also excluded tumors with characteristics we considered may influence the results, as well as stage IV patients, as different predictive factors have been identified in them [3].

However, we must not forget that CRC is a heterogeneous disease, and hence we insist on the convenience of attaining the most homogeneous study samples possible to obtain new predictive models that improve on current ones, which are unable to explain how patients in the same pathological stage have a different evolution.

We are aware that, because of this heterogeneity, there is great difficulty in integrating all of the available prognostic information to make a precise, individualized estimate of the evolution of patients with CRC.

There are many predictive nomograms in patients with CRC, most of them in patients in stage IV, and very few incorporate serological markers [5, 8]; in addition, we have found none which include clinical variables. And so, in our statistical analysis, as well as analyzing the histological factors established in the literature, we have jointly examined clinical variables and serological markers with the aim of identifying new prognostic factors.
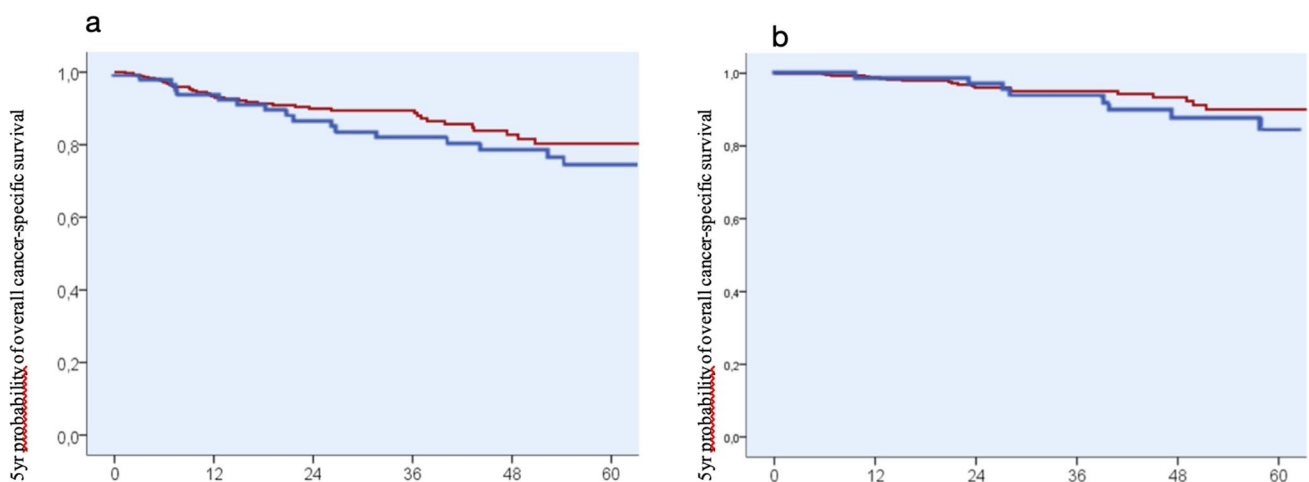
Fig. 3 Calibration curves for 5 year disease-free survival (**a**) and 5 year overall cancer-specific survival (**b**) using nomograms with clinicopathological and preoperative serological tumor markers.

Comparing the curves of recurrence and survival at 5 years according to the model (red curve) with the curves observed (blue curve) (Color figure online)

In this research, we studied the prognostic role of the clinical manifestations of patients with CRC alongside the rest of the histopathological and serological variables, as none of the papers included in the review published by Mahar et al. [9] on CRC predictive nomograms includes clinical variables. Our results show that the presence of blood in stools (rectal bleeding or hematochezia) as a first symptom of CRC was the only clinical variable related to the overall CSS in the multivariate analysis, presenting itself as a protective factor ($p < 0.06$; HR 0.24, IC95% = 0.05–1.04). The association between the presence of gastrointestinal bleeding and overall survival (OS) has been described previously by other authors, but upon analyzing this symptom with the set of variables in the multivariate analysis, they found no relation with OS at 5 years [10].

Many groups have expressed interest in the prognostic value of markers in peripheral blood in patients with CRC, as representatives of preoperative chronic inflammatory status. With this objective, low-cost biomarkers have been described which can easily be incorporated into routine clinical practice to optimally predict the prognosis of patients with CRC and guide treatment, such as NLR, PLR and LMR.

In this study, after analyzing the prognostic role of several preoperative serological markers, only PLR proved to be an independent predictor of DFS and overall CSS. These results concur with those obtained by Nan Chen and collaborators [12] in a recent meta-analysis, although we must take into account the fact that many studies include patients with stage IV disease. In another meta-analysis from 2017, the conclusions were similar, relating high PLR values with worse OS and DFS, but on performing a secondary group analysis to deal with the heterogeneity of the studies included, the PLR only revealed a relation to the OS [13]. We have not analyzed the OS, as we considered it may be influenced by the age and comorbidities of the patients with CRC. None of the studies included in the two last meta-analyses of patients with CRC in stage I-III have as their objective the study of overall CSS [11, 12].

The actual mechanisms by which a high PLR value influences the prognosis of patients with CRC have not been fully clarified. Thrombocytosis and lymphopenia, associated with a drop in cancer immunity, are some of the mechanisms proposed [12].

With regard to the histological variables analyzed, perineural invasion and nodal status were the variables related to the prognosis of patients with CRC.

Several authors have demonstrated the prognostic value of lymphatic, vascular and perineural invasion (PNI) in patients with CRC, but none of these three types of invasion has been included in any prognostic nomogram published [13]. This research study confirms that PNI is an independent risk factor for recurrence. The mechanisms that explain the correlation between tumor progression and the existence of PNI are not fully defined [14].

Based on the variables left in the DFS and overall CSS models after the multivariate analysis using the Cox regression model, we have created two predictive nomograms of DFS and overall CSS at 5 years (Figs. 1 and 2). As we can see in the results from this research study, as well as some of the histological variables established, the two nomograms created include serological and clinical markers. We have taken into account the main critique made by Mahar et al. [9] regarding the lack of quality of the prognostic systems available, which limits their practical application in our daily clinic. For this reason, we felt it was necessary to perform an internal and external validation according to the latest recommendations of the TRIPOD guidelines [7]. The internal validation was performed using bootstrapping; only 10% of the nomograms included in the review published by Mahar et al. use this validation method, which is the recommended one. Similarly, over half of the nomograms did not conduct an adequate external validation by means of calibration and discrimination. In our study, the calibration measurements used were general calibration and the calibration slope (comparing the curves of recurrence and survival at 5 years according to the model with the curves observed), and the discriminative capacity of each model using Harrell's C statistic. The Harrell's C indices were 0.82 and 0.83 to predict DFS and overall CSS at 5 years, respectively; an index of above 0.6 is considered adequate. Meanwhile, on the calibration graphs of our study, we can see that there are no differences in the DFS curves estimated by the nomogram compared to the actual one, but for overall CSS we find a pronounced difference in the survival curves, which reveals a good predictive capacity of the DFS nomogram, but not for the overall CSS nomogram. These differences may be due to the small sample size, or to other differences between our population and the validation population, which cannot be controlled, such as the different teams of surgeons and pathologists, and differences in follow-up protocols.

Conclusion

We have created a predictive model of DFS and overall CSS at 5 years with data that is easily available which can help personalize the treatment and follow-up of patients with CRC. The peculiarity of our nomograms is that they jointly integrate clinical, analytical and histological variables, and that the data are from a homogeneous group of patients with CRC. We also conducted adequate internal and external validation.

Data availability statement All data supporting the findings of this study are available from corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest. The authors declare that they have no use of off-label or unapproved drugs or products. The authors declare that they have no use of previously copyrighted material. The authors declare that no funding has been received for the conduct of this study and/or preparation of this manuscript. The authors declare that this paper is not currently under review by another journal; and the paper has not been accepted for publication elsewhere.

Ethical Approval This paper has been approved by Ethics committee of our Hospital.

Research involving human participants and/or animals This research not involving human participants or animals.

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