Received: 1 May 2025 | Revised: 9 September 2025 | Accepted: 17 September 2025

DOI: 10.1111/codi.70250

ORIGINAL ARTICLE

Long-term prognostic implications of type 2 diabetes mellitus in colorectal cancer patients

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Funding information
Instituto de Salud Carlos III, Grant/Award Number: PI13/0013;PI18/01181, PI21/252, PI13/01692, PI18/01589 and CD22/0053

Abstract

Aim: Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. Epidemiological evidence has identified Type 2 Diabetes Mellitus (T2DM) as a risk factor for CRC. This study aimed to evaluate the impact of T2DM, along with clinicopathological and socio-demographic factors, on long-term overall survival in a large, nationally representative cohort of CRC patients with T2DM.

Method: A prospective cohort of 1186 CRC patients was analysed, approximately 20% of whom had a diagnosis of T2DM. Kaplan–Meier estimates and multivariable Cox proportional hazards models were used to assess overall survival.

Results: CRC patients with T2DM were more often older, had lower educational attainment, were former smokers, and presented higher comorbidity, right-sided tumours, prior symptoms, depressive symptoms, elevated Body Mass Index (BMI) and lower baseline quality of life (EORTC QLQ-C30 < 75). In multivariable analysis, the co-occurrence of T2DM and depression ($p = 0.007$; HR 1.77; 95% CI: 1.17–2.68) and low quality of life ($p = 0.04$; HR 1.42; 95% CI: 1.02–1.97) emerged as independent predictors of poorer long-term survival.

Conclusion: Our findings highlight the compounded negative impact of T2DM and depression on overall survival in CRC patients. Their combined presence significantly worsens prognosis, underscoring the need for integrated care approaches that address both physical and mental health. Future research should explore targeted interventions for these comorbidities to improve long-term outcomes and quality of life in this high-risk population.

KEYWORDS
colorectal cancer, depression, diabetes mellitus, risk factor, survival

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For affiliations refer to page 8.

INTRODUCTION

Colorectal cancer (CRC), encompassing both colon and rectal malignancies, represents a major global health challenge due to its high incidence and mortality rates. Accounting for approximately 10% of all cancer diagnoses, CRC ranks among the most prevalent cancers worldwide, with over 1.8 million new cases reported annually [1]. In 2020, CRC ranked as the third most commonly diagnosed cancer after breast and lung cancers and the second leading cause of cancer-related deaths, resulting in approximately 935,000 deaths [1, 2]. These figures underscore the urgent need to better understand and manage risk factors influencing CRC incidence and survival outcomes.

While survival rates for CRC in Spain are projected to improve by 2025, largely due to the broader implementation of population-based screening programs [3], the incidence of CRC continues to rise. This trend is strongly linked to shifts in lifestyle behaviours that elevate CRC risk, including higher consumption of processed foods and alcohol, physical inactivity, smoking and the increasing prevalence of obesity [1]. Notably, the global surge in obesity and type 2 diabetes mellitus (T2DM) has paralleled rising cancer incidence rates, fuelled by environmental changes, sedentary behaviours and population aging [4]. Consistent with the growing recognition of metabolic disorders like T2DM as contributors to cancer development, an increasing proportion of cancer patients present with these comorbid conditions [4].

Specifically, epidemiological studies consistently report that T2DM is associated with a heightened risk of developing CRC [5, 6], with coexistence rates ranging from 5 to 26% [7]. Furthermore, 20%–40% of individuals with T2DM are at greater risk for CRC and often face worse prognoses than those without T2DM [8], partly due to a greater burden of comorbidities, including cardiovascular, renal and hepatic diseases, that complicate cancer management, reduce treatment adherence and increase the risk of treatment-related complications [9].

Beyond physiological factors, growing evidence indicates that psychosocial factors, particularly anxiety and depression, can also adversely affect cancer outcomes. Notably, depression and T2DM frequently co-occur, with evidence supporting a bidirectional relationship particularly strong for depression predicting diabetes [10]. Besides biological pathways such as systemic inflammation, immune dysregulation and neuroendocrine dysfunction, behavioural factors like reduced treatment adherence and delayed healthcare-seeking have been implicated in this association [11–13]. Given the multifactorial nature of CRC, shaped by the complex interplay of clinical, pathological, psychosocial and demographic factors, a comprehensive and integrative approach is essential to fully understand survival disparities and improve patient care.

The increasing prevalence of T2DM and its frequent coexistence with CRC offer a unique opportunity to investigate how physical and psychosocial factors jointly affect survival outcomes. This study aimed to assess the prognostic impact of T2DM on 5-year overall survival in a large, nationally representative cohort of CRC patients and to explore its interaction with clinical, pathological and psychosocial variables, with the goal of informing more integrated and individualized care strategies.

What does this paper add to the literature?

This study identifies key long-term prognostic factors in CRC patients with T2DM, showing that the co-occurrence of diabetes and depression increases mortality risk by 77%, underscoring the importance of integrated physical and mental health care to improve survival and quality of life in this high-risk population.

PATIENTS AND METHODS

Study design, scope and period of study

This prospective, multicentre, observational study relied on patient clinical data records for data collection. A total of 1186 patients were recruited between 2010 and 2012 from 22 hospitals across six Autonomous Communities within the Spanish national public health system. Eligible participants were individuals diagnosed with colon cancer (tumours located more than 15 cm above the anal margin) or rectal cancer (tumours located 15 cm or less from the anal margin), encompassing TNM stages I to IV (AJCC-7th edition), who underwent initial curative and/or palliative surgery, either elective or urgent, between 2010 and 2012. Participants were excluded if they had in situ colon or rectal tumours, were considered inoperable, were unable to respond to questionnaires due to severe mental or physical conditions, had a terminal illness, had a history of prior radiotherapy or chemotherapy for CRC or another malignancy or had missing data regarding sex, age, tumour location, tumour invasion, previous screening tests, prior symptomatology, quality of life (EORTC QLQ-C30) or survival outcome. Patients with stage IV CRC were included only if metastases were diagnosed de novo and no previous oncological treatment had been administered.

Ethics

This study was approved by the corresponding institutional review boards of the participating hospitals, as well as by the Andalusian Regional Committee of Clinical Trials of Andalusia (IRYSS-CCR, December 3, 2009). All patients were previously informed about the objectives of the study and provided a signed informed consent in accordance with current regulations (Principles of the Declaration of Helsinki, Title 45, U.S. Code of Federal Regulations, Part 46,

Protection of Human Subjects, Revised November 2001, effective December 13, 2001).

Data collection and variables included in the study

Clinical data at the time of diagnosis were collected directly from medical records and databases by qualified reviewers. This process adhered to a standardized data collection and an instruction manual. Patients were prospectively and consecutively included in the study from each participating hospital, and tumour diagnosis was relied on anatomopathological findings post-biopsy via colonoscopy.

Study variables: Socio-demographic variables included sex, age and educational level. Clinical-pathological variables comprised body mass index (BMI), smoking habit, alcohol consumption, Charlson Comorbidity Index (excluding diabetes), tumour location, clinical stage according to the TNM classification (AJCC-7), carcinoembryonic antigen (CEA) levels, history of previous screening, 5-year tumour recurrence and presence of tumour invasion, defined as pathological evidence of invasion beyond the bowel wall into adjacent structures and/or extramural vascular invasion (EMVI).

Patient-reported variables included prior symptomatology, anxiety and depressive symptoms as measured by the Hospital Anxiety and Depression Scale (HADS-A and HADS-D questionnaires, respectively) [14], and quality of life assessed using the EORTC QLQ-C30 version 2.0 questionnaire [15]. *KRAS* status was not included in the analysis due to a significant amount of missing data, with 1079 patients (90.97% of total sample) lacking *KRAS* testing results. This limitation is attributed to the fact that the data were collected from a cohort prior to the systematic analysis of *KRAS* status within the public hospital healthcare services.

Primary outcome variable was 5-year overall survival, defined as the time (in months) from histological diagnosis to death or the last follow-up visit.

Statistical analysis

We conducted a descriptive analysis for quantitative variables using measures of central tendency, dispersion and position, while qualitative variables were summarized through frequency distributions. Bivariate analysis was conducted using diabetes status as the grouping variable. Differences in qualitative variables were assessed with the chi-square test, while quantitative variables were compared using Student's *t*-test.

Kaplan–Meier survival curves were generated to assess the survival probabilities based on diabetes status, HADS-D depressive symptomatology, and their combined effect. Statistical significance among the defined groups was assessed using the log-rank test.

To evaluate overall survival, a multivariable Cox proportional hazards regression model was applied using a backward stepwise selection method. Statistical significance was set at $p<0.05$ for all tests, although the significance threshold for variable inclusion in the multivariable model was set at $p=0.2$ [16]. Hazard Ratios (HR) and their corresponding 95% confidence intervals (95% CI) were reported. Model discrimination was assessed using Harrell's C-index, computed with 2000 bootstrap resamples to ensure robustness. A number >0.70 was deemed indicative of acceptable model discrimination. All analyses were performed using IBM SPSS Statistics, version 28. Figures were depicted with R statistical software, 4.2 release.

RESULTS

Clinical and pathological characteristics of the study population

The socio-demographic and clinical characteristics of the 1186 patients included in the study are summarized in Table 1. Of the total cohort, 63.2% were male, and 20% had T2DM. Compared to patients without T2DM, those with T2DM were significantly older ($p<0.001$), had higher BMI values ($p<0.001$), lower educational attainment ($p=0.002$) and higher Charlson Comorbidity Index scores ($p=0.004$). They were also more likely to present with right-sided tumours ($p=0.015$) and prior symptomatology at diagnosis ($p=0.035$).

Depressive symptoms, as measured by the HADS-D scale, were more common among patients with T2DM ($p=0.009$), with a significant association between coexisting T2DM and depression ($p<0.001$), whereas anxiety symptoms (HADS-A) did not show a significant association. Patients with T2DM also reported lower baseline quality of life scores on the EORTC QLQ-C30 ($p<0.001$). Although 5-year recurrence rates did not differ significantly between groups, patients with T2DM had a higher 5-year mortality rate (64% vs. 73.7%; $p=0.004$) (Table 1).

Survival analysis based on type 2 diabetes mellitus and depressive symptoms

To assess the impact of T2DM on overall survival, we conducted a Kaplan–Meier survival analysis for 5-year mortality, stratifying by diabetes status. Patients with T2DM demonstrated significantly lower 5-year survival compared to those without T2DM ($p=0.0023$) (Figure 1).

Kaplan–Meier analysis was also conducted to assess the prognostic impact of depressive symptoms, using HADS-D scores. Patients with depressive symptoms (HADS-D ≥ 8) exhibited significantly lower overall survival compared to those without depressive symptoms (HADS-D < 8) ($p<0.001$) (Figure 2).

Survival analysis based on the combined presence of TD2M and depressive symptoms

To explore the combined impact of T2DM and depressive symptoms (HADS ≥8) on overall survival, a composite variable was created,

TABLE 1 Socio-demographic and clinical characteristics of the recruited sample by diabetes status.

		Type 2 diabetes mellitus		
	Total ($N = 1186$)	No ($N = 958$)	Yes ($N = 228$)	*p* Value
Exposure variables				
Sex				
Male	749 (63.2)	593 (61.9)	156 (68.4)	0.066
Female	437 (36.8)	365 (38.1)	72 (31.6)	
Age[a]				
Mean (SD)	67.59 (10.80)	66.87 (11.14)	70.64 (8.61)	**<0.001**
Educational level				
No formal – primary	860 (75.2)	677 (73.3)	183 (83.2)	**0.002**
Secondary – university	284 (24.8)	247 (26.7)	37 (16.8)	
Body mass index (BMI)[a]				
Mean (SD)	27.61 (4.58)	27.34 (4.49)	28.74 (4.76)	**<0.001**
Min–max	15.82–54.67	15.82–54.67	19.38–51.98	
Smoking habit				
Never smoked	554 (48.2)	451 (48.6)	103 (46.6)	**0.003**
Current smoker	151 (13.1)	135 (14.5)	16 (7.2)	
Former smoker	444 (38.6)	342 (36.9)	102 (46.2)	
Alcohol consumption				
No	987 (86.7)	793 (86.7)	194 (87.0)	0.897
Yes	151 (13.3)	122 (13.3)	29 (13.0)	
Charlson Index without T2DM[b]				
Median (IQR)	2.00 (2.00–3.00)	2.00 (2.00–3.00)	2.00 (2.00–3.00)	**0.004**
Tumour location				
Right-sided	348 (29.3)	266 (27.8)	82 (36.0)	**0.015**
Left-sided or rectum	838 (70.7)	692 (72.2)	146 (64.0)	
Clinical Stage (TNM)				
I	261 (22.0)	211 (22.0)	50 (21.9)	0.257
II	420 (35.4)	335 (35.0)	85 (37.3)	
III	386 (32.5)	322 (33.6)	64 (28.1)	
IV	119 (10.0)	90 (9.4)	29 (12.7)	
Extramural vascular invasion (EMVI)				
No	615 (65.45)	504 (66.1)	111 (62.4)	0.337
Yes	325 (34.57)	258 (33.9)	67 (37.6)	
Perineural invasion				
No	785 (83.1)	637 (82.9)	148 (83.6)	0.8296
Yes	160 (16.9)	131 (17.1)	29 (16.4)	
Lymphatic invasion				
No	738 (80.0)	604 (80.5)	134 (77.9)	0.4370
Yes	184 (20.0)	146 (19.5)	38 (22.1)	
Previous screening				
No	915 (82.9)	739 (83.3)	176 (81.1)	0.439
Yes	189 (17.1)	148 (16.7)	41 (18.9)	
Prior symptomatology				
No	154 (13.1)	134 (14.1)	20 (8.8)	**0.035**
Yes	1026 (86.9)	819 (85.9)	207 (91.2)	

TABLE 1 (Continued)

	Total ($N = 1186$)	Type 2 diabetes mellitus		p Value
		No ($N = 958$)	Yes ($N = 228$)	
Anxiety HADS-A				
<8	704 (59.4)	576 (60.1)	128 (56.1)	0.294
≥8	482 (40.6)	382 (39.9)	100 (43.9)	
Depression HADS-D				
<8	920 (77.6)	758 (79.1)	162 (71.1)	**0.009**
≥8	266 (22.4)	200 (20.9)	66 (28.9)	
Depression and or T2DM				
No diabetes with HADS-D <8	758 (63.9)	758 (79.1)		**<0.0001**
No diabetes with HADS-D ≥8	200 (16.9)	200 (20.9)		
Diabetes with HADS-D <8	162 (13.7)		162 (71.1)	
Diabetes with HADS-D ≥8	66 (5.6)		66 (28.9)	
Baseline quality of life (EORTC QLQ-C30)				
<75	345 (30.45)	258 (27.98)	87 (41.23)	**<0.001**
75–90	429 (37.86)	347 (37.64)	82 (28.86)	
>90	359 (31.69)	317 (34.38)	42 (19.91)	
Outcome variables				
5-year recurrence				
No	1105 (93.2)	886 (92.5)	219 (96.1)	0.055
Yes	81 (6.8)	72 (7.5)	9 (3.9)	
5-year mortality				
Alive	852 (71.8)	706 (73.7)	146 (64.0)	**0.004**
Exitus	334 (28.2)	252 (26.3)	82 (36.0)	

Note: Values are presented as *n* (%) unless otherwise specified. Continuous variables are expressed as mean (standard deviation)[a] or median (interquartile range)[b], as indicated. *p* Values reflect comparisons between patients with and without Type 2 Diabetes Mellitus. Statistically significant results ($p < 0.05$) are shown in bold.

categorizing patients into four groups based on diabetes and depressive symptom status. Kaplan–Meier analysis showed significant survival differences ($p < 0.0001$), with patients exhibiting both T2DM and depressive symptoms (HADS-D ≥8) having the poorest 5-year survival, while those without either T2DM condition consistently showed the highest survival probability. Intermediate survival outcomes were observed in patients with either T2DM alone or depressive symptoms alone (Figure 3).

Multivariable analysis of prognostic factors

In the multivariable analysis, beyond the strong impact of advanced tumour stage (HR 9.59; 95% CI: 6.32–14.44; $p < 0.001$), the coexistence of T2DM and depressive symptoms (HADS-D ≥8) emerged as an independent prognostic factor, associated with a 77% increased risk of death (HR 1.77; 95% CI: 1.17–2.68; $p = 0.007$), highlighting the compounded impact of physical and mental health on CRC outcomes.

Additionally, low baseline quality of life (EORTC QLQ-C30 score <75) was independently associated with poorer survival (HR 1.42; 95% CI: 1.02–1.97; $p = 0.04$), emphasizing the prognostic relevance of patient-reported outcomes.

Other independent predictors of worse survival included male sex (HR 1.34; 95% CI: 1.05–1.72; $p = 0.02$), older age (HR 1.04 per year; 95% CI: 1.03–1.05; $p < 0.001$) and a higher Charlson Comorbidity Index excluding diabetes (HR 1.23; 95% CI: 1.14–1.33; $p < 0.001$) (Table 2).

DISCUSSION

Epidemiological studies have consistently identified T2DM as a significant risk factor for CRC, associated with increased overall mortality, higher incidence and greater recurrence rates among patients [17–23]. However, it remains unclear whether this association is primarily driven by shared risk factors such as depression and obesity [24, 25].

To better capture the spectrum of metabolic risk, our study analysed BMI as a continuous variable. Despite detecting a high prevalence of both elevated BMI and depressive symptoms in patients with T2DM, only depression emerged as an independent predictor for

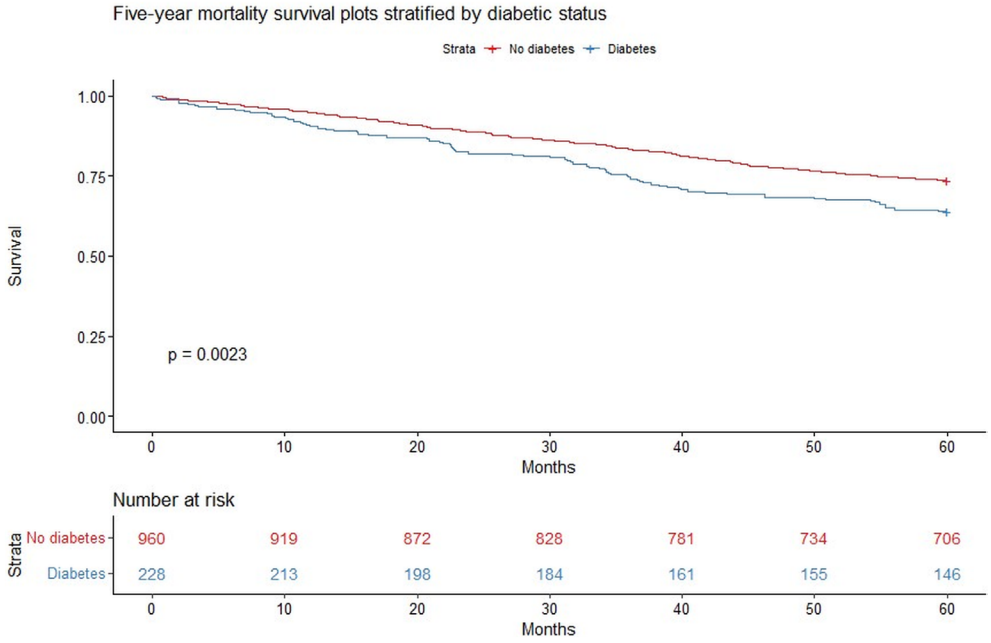

FIGURE 1 Five-year Kaplan–Meier survival curves for CRC patients stratified by diabetes status, showing lower survival in patients with diabetes compared to those without ($p = 0.0023$). At baseline, 960 patients had no T2DM and 228 had T2DM; by the end of the 5-year follow-up, 706 and 146 patients remained at risk, respectively.

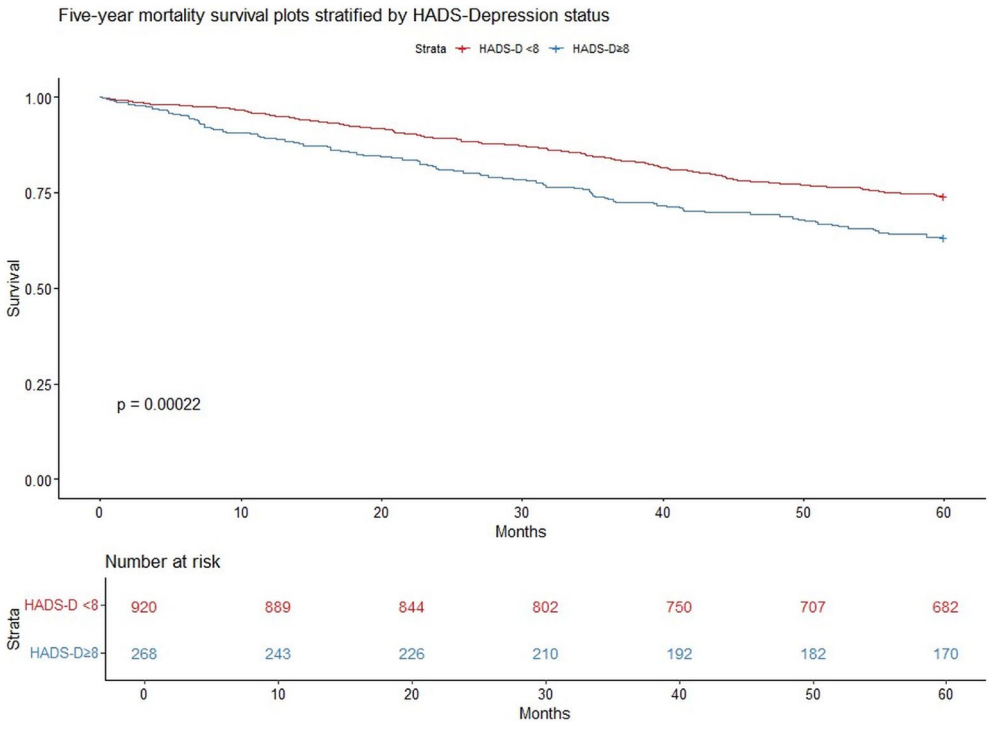

FIGURE 2 Kaplan–Meier survival curves for CRC patients, stratified by depressive symptoms (HADS-D ≥8 indicating depression), show significantly lower survival probabilities in those with depressive symptoms. At baseline, 920 patients had no depressive symptoms, and 266 had depressive symptoms. By the end of the 5-year follow-up, the number of patients at risk decreased to 682 and 170, respectively, reflecting a consistent decline in survival across both groups.

long-term overall mortality in the multivariable analysis. This finding aligns with previous studies linking depression to poorer survival in CRC [11, 26, 27] and, to our knowledge, this is the first study to report both the higher incidence of depressive symptoms and their impact on 5-year overall survival in those with T2DM, highlighting the importance of integrating routine psychological assessment and intervention into standard CRC care, as addressing depressive symptoms may significantly improve both quality of life and survival in high-risk patients.

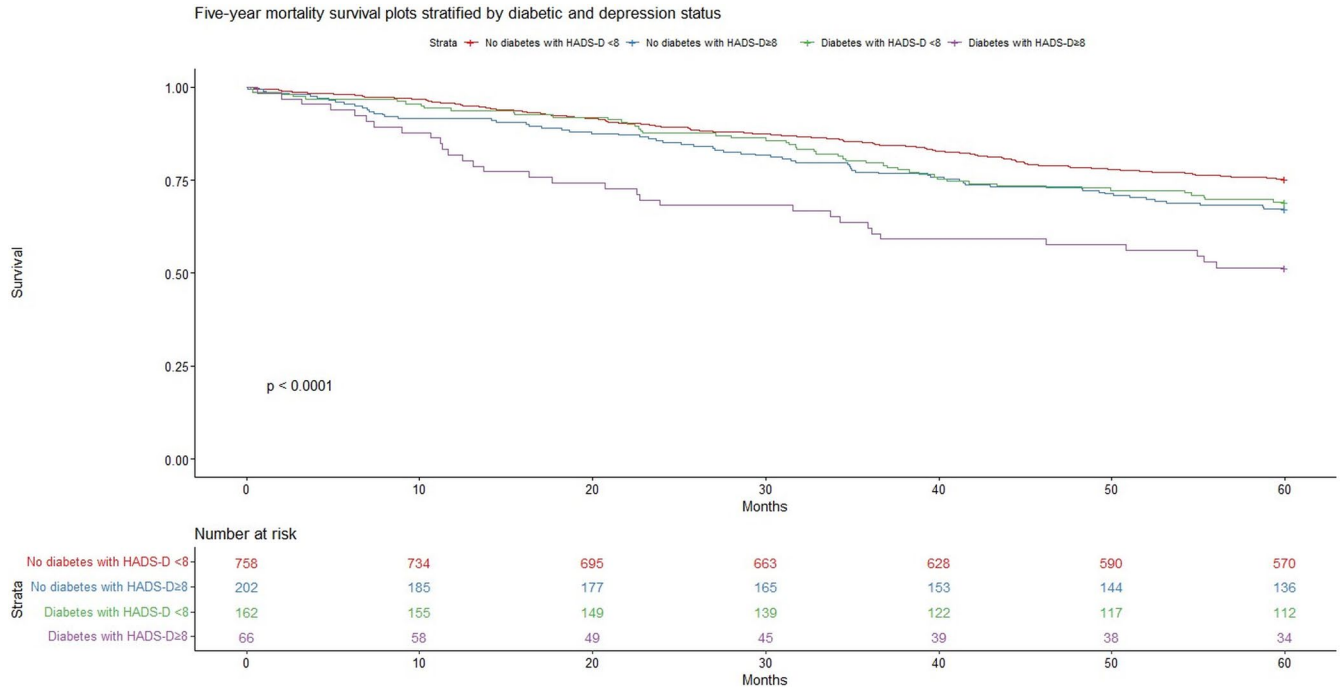

FIGURE 3 Kaplan–Meier curves for CRC patients stratified by diabetes status and depressive symptoms (HADS-D ≥8). Patients without T2DM and without depressive symptoms showed the best survival, whereas those with both conditions experienced the lowest survival rates ($p < 0.0001$). At baseline, the number of patients at risk in each group was 734 for those without T2DM and without depressive symptoms, 185 for those without T2DM but with depressive symptoms, 155 for those with T2DM but without depressive symptoms, and 58 for those with both T2DM and depressive symptoms. By the 5-year follow-up, these numbers declined to 590, 144, 117 and 38, respectively, reflecting a progressive decline in survivors across all groups.

Moreover, our study highlights that both the co-occurrence of T2DM and depression, as well as reduced baseline patient-reported quality of life, is significant independent risk factors for poorer long-term overall survival in CRC patients, underscoring the limitations of a cancer-only treatment focus [9] and emphasizing the need for multidisciplinary care that integrates oncology, endocrinology and psychosocial support, particularly in long-term survivors where co-morbidities like T2DM and depression may outweigh tumour-related factors in determining prognosis.

Our findings are consistent with prior research showing that CRC patients with T2DM tend to be older [6, 28], have a higher BMI, be former smokers, and have lower educational attainment [6]. Additionally, we found that many of these patients presented with cancer-related symptoms before diagnosis, which justifies the implementation of targeted preventive interventions, such as raising awareness, promoting lifestyle changes, offering dietary guidance and increasing physical activity, particularly in lower socioeconomic and educational communities, to enhance patient quality of life and outcomes.

T2DM was significantly associated with poorer 5-year survival outcomes, with patients exhibiting markedly lower survival rates than those without diabetes. Beyond its role in CRC carcinogenesis, progression and recurrence, T2DM increases mortality risk through associated comorbidities such as hypertension, dyslipidaemia and cardiovascular or microvascular complications [29]. Additionally, T2DM may complicate CRC treatment, as affected patients are often less likely to receive optimal therapies, may undergo dose reductions, face treatment delays or discontinuations and are at higher risk for post-surgical complications, all of which can compromise treatment efficacy and worsen both short- and long-term outcomes [9]. The substantial prognostic burden of comorbidities reinforces the need for multidisciplinary and coordinated management, with a strong emphasis on patient education, medication adherence, lifestyle modifications and consistent monitoring to mitigate the risks associated with poorly controlled hyperglycaemia. Such an approach may enhance survival and quality of life in patients with localized CRC and optimize therapeutic strategies in those with metastatic disease.

Despite the strengths of our study, including a large, nationally representative cohort, several limitations must be acknowledged. Although recent evidence suggests associations between diabetes and tumour characteristics as *BRAF* mutations or microsatellite instability (MSI-high status) [30], we were unable to assess these variables due to substantial missing data. This was largely attributable to data collection preceding the routine implementation of molecular testing protocols in public healthcare settings. Additionally, we could not evaluate longitudinal glycaemic control through serial haemoglobin A1c measurements, nor assess visceral adiposity or modern lifestyle factors such as dietary habits, as these were not included in the original study protocol (IRYSS-CCR). Finally, the analysis of disease-specific mortality was not feasible due to incomplete data. Future research using updated cohorts should aim to incorporate these variables to more fully elucidate the complex interactions between T2DM and CRC outcomes.

TABLE 2 Adjusted Cox-Regression Model for 5-year follow-up mortality prediction.

Variables	Beta (SE)	Hazard ratio	95% CI		*p* Value
			Lower	Upper	
Age	0.04 (0.006)	1.04	1.03	1.05	**<0.001**
Sex: male	0.29 (0.13)	1.34	1.05	1.72	**0.02**
Body mass index (BMI)	0.02 (0.01)	1.02	0.99	1.05	0.08
Charlson index (without diabetes)	0.21 (0.04)	1.23	1.14	1.33	**<0.001**
Clinical tumour stage (TNM)					
I	Reference				
II	0.35 (0.21)	1.42	0.94	2.14	0.10
III	1.15 (0.20)	3.16	2.15	4.66	**<0.001**
IV	2.26 (0.21)	9.59	6.32	14.55	**<0.001**
Diabetes & depression (HADS-D)					
No diabetes with HADS-D <8	Reference				
No diabetes with HADS-D ≥8	0.18 (0.17)	1.20	0.86	1.66	0.282
Diabetes with HADS-D <8	0.21 (0.16)	1.24	0.90	1.71	0.19
Diabetes with HADS-D ≥8	0.57 (0.21)	1.77	1.17	2.68	**0.007**
Baseline EORTC QLQ-C30					
<75	0.35 (0.17)	1.42	1.02	1.97	**0.04**
75–90	0.21 (0.15)	1.23	0.92	1.65	0.17
>90	Reference				
C-index (95% CI)	0.75 (0.70, 0.78)				

Abbreviations: Beta (SE), Coefficient and the standard error; CI, Confidence interval; EORTC QLQ-C30, Quality of life questionnaire total score; HADS-D, Depression score of the Hospital Anxiety Depression questionnaire.

Statistically significant results ($p < 0.05$) are shown in bold.

CONCLUSION

This study highlights the significant impact of both T2DM and depressive symptoms, individually and synergistically, on 5-year overall survival in patients with CRC. The co-occurrence of these conditions was associated with a markedly worse prognosis, emphasizing the compounded burden of metabolic and mental health comorbidities on cancer outcomes. Additionally, reduced baseline-reported quality of life emerged as an independent prognostic factor, reinforcing the need to address physical, psychological and social dimensions in CRC care. Our findings underscore the importance of implementing multidisciplinary care models that integrate oncology, endocrinology and mental health services to improve survival and quality of life in this high-risk population. Future research should aim to develop and assess targeted, holistic interventions that address the interplay between metabolic dysfunction, mental health and cancer progression.

AUTHOR CONTRIBUTIONS

Julia Alcaide-Garcia: Conceptualization; investigation; writing – original draft; visualization; methodology. **Hatim Boughanem:** Conceptualization; investigation; methodology; visualization; writing – review and editing. **Marilina García-Aranda:** Conceptualization; investigation; methodology; visualization; writing – review and editing; writing – original draft. **Francisco Rivas-Ruiz:** Conceptualization; investigation; methodology; formal analysis. **Urko Aguirre:** Investigation; methodology; formal analysis; software. **Desiree Martín García:** Investigation; writing – review and editing; data curation. **María Padilla-Ruiz:** Data curation; investigation. **Esperanza Varela-Moreno:** Investigation; writing – review and editing; data curation. **Marta Robles-Lasarte:** Investigation; writing – review and editing. **Isabel del Cura:** Investigation; conceptualization; funding acquisition; supervision; project administration. **Marisa Baré:** Conceptualization; investigation; funding acquisition; project administration; supervision. **María M. Morales-Suárez Varela:** Conceptualization; investigation; funding acquisition; project administration; supervision. **José M. Quintana:** Conceptualization; investigation; funding acquisition; project administration; supervision. **Manuel Macías:** Conceptualization; investigation; writing – review and editing; supervision. **Maximino Redondo:** Conceptualization; investigation; funding acquisition; writing – review and editing; supervision.

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FUNDING INFORMATION

This work was supported in part by grants from the Instituto de Salud Carlos III and the European Regional Development Fund (PS09/00314, PS09/00910, PS09/00746, PS09/00805, PI09/90460, PI09/90490, PI09/90453, PI09/90441, PI09/90397); and the thematic network—REDISSEC (Red de Investigación en Servicios de Salud en Enfermedades Crónicas)—of the Instituto de Salud Carlos III. HB is supported by a 'Sara Borrell' postdoctoral contract (CD22/00053) from the Instituto de Salud Carlos III – Madrid (Spain), *'Financiado por la Unión Europea – NextGenerationEU' y mediante el Plan de Recuperación, Transformación y Resiliencia*.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee Costa del Sol, under protocol number IRYSS-CCR, December 3, 2009. Written informed consent was obtained from all participants prior to their inclusion in the study.

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How to cite this article: Alcaide-Garcia J, Boughanem H, García-Aranda M, Rivas-Ruiz F, Aguirre U, García DM, et al. Long-term prognostic implications of type 2 diabetes mellitus in colorectal cancer patients. Colorectal Dis. 2025;27:e70250. https://doi.org/10.1111/codi.70250

APPENDIX A

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