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Original Research

Multimorbidity and short-term overall mortality among colorectal cancer patients in Spain: A population-based cohort study

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Abstract ***Background:*** Numerous studies have analysed the effect of comorbidity on cancer outcomes, but evidence on the association between multimorbidity and short-term mortality among colorectal cancer patients is limited. We aimed to assess this association and the most frequent patterns of multimorbidity associated with a higher short-term mortality risk among colorectal cancer patients in Spain.
Methods: Data were obtained from two Spanish population-based cancer registries and electronic health records. We estimated the unadjusted cumulative incidence of death by

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comorbidity status at 6 months and 1 year. We used a flexible parametric model to derive the excess mortality hazard ratios (HRs) for multimorbidity after adjusting for sex, age at diagnosis, cancer stage and treatment. We estimated the adjusted cumulative incidence of death by comorbidity status and identified multimorbidity patterns.

Results: Among the study participants, 1,048 cases were diagnosed with cancers of the colon and rectum, 2 cases with cancer of the anus with overlapping sites of the rectum and 11 cases with anal adenocarcinomas but treated as colorectal cancer patients. Among 1,061 colorectal cancer patients, 171 (16.2%) died before 6 months, 246 (23.3%) died before the 1-year follow-up, and 324 (30.5%) had multimorbidity. Patients with multimorbidity had two times higher mortality risk than those without comorbidities at 6 months (adjusted HR: 2.04; 95% confidence interval [CI]: 1.30–3.20, p = 0.002). The most frequent multimorbidity pattern was congestive heart failure + diabetes. However, patients with rheumatologic disease + diabetes had two times higher 1-year mortality risk than those without comorbidities (HR: 2.23; 95% CI: 1.23–4.07, p = 0.008).

Conclusions: Multimorbidity was a strong independent predictor of short-term mortality at 6 months and 1 year among the colorectal cancer patients in Spain. The identified multimorbidity pattern was consistent. Our findings might help identify patients at a higher risk for poor cancer and treatment outcomes.

1. Introduction

In 2018, there were 9.6 million deaths from cancer worldwide, making cancer the second cause of death globally [1]. In Spain, colorectal cancer (CRC) is the most commonly diagnosed cancer, especially among the elderly [2]. The rise in chronic non-communicable diseases such as cancer, heart disease and diabetes reflects lifestyle and diet changes and ageing. In Western countries, the rapidly increasing costs of managing non-communicable diseases including cancer have affected economic growth [3]. Cancer incidence is expected to accelerate in the coming decades in Europe, largely because of global ageing. However, older people are under-represented in clinical trials, mainly due to the higher multimorbidity prevalence among this group [4].

Comorbidity refers to the presence of a long-term health condition or disorder concomitant with a primary disease such as cancer [5], while multimorbidity refers to the existence of two or more comorbid conditions [6]. In the elderly, comorbidity and multimorbidity are increasingly perceived as a health issue [7,8]. Evidence shows that comorbidities might influence cancer treatment options, outcomes and overall survival [9,10].

We hypothesised that multimorbidity could be associated with a higher mortality risk 6 months and 1 year after a CRC diagnosis. However, evidence on the association of multimorbidity with short-term CRC survival is limited [11,12]. Therefore, we aimed to assess the association between multimorbidity and short-term mortality and describe the most frequent patterns of multimorbidity associated with a higher short-term mortality risk among CRC patients in Spain.

2. Materials and methods

2.1. Study design, participants, data and setting

This population-based cohort study included patients diagnosed with CRC in 2011 in Girona and Granada, Spain. The diagnoses were based on codes C18–C21 according to the International Classification of Diseases for Oncology, 3rd Edition. The entry date of each patient into the cohort was defined as the date of cancer diagnosis, and their exit date was defined as the date of death or the date at 6 months or 1 year after their cancer diagnosis, whichever occurred first.

Data were obtained retrospectively from two Spanish population-based cancer registries and patients' electronic health records. The data collection followed a detailed protocol from the European High-Resolution studies collaboration (TRANSCAN-HIGHCARE project within the ERA-Net) [13]. We recorded information on cancer stage at diagnosis (TNM staging system, 7th edition), comorbidities, sex, type of surgery, chemotherapy and vital status. Vital status for all CRC patients was assessed at 6 months and 1 year after cancer diagnosis and was ascertained based on information from clinical records linked to the national death registry of the Spanish National Statistics Institute (INE).

Comorbidities were assessed from the electronic health records based on codes from the International Classification of Diseases, 10th Revision (Supplementary Table S1). All recorded comorbidities were included except for those comorbidities diagnosed within 6 months before of cancer diagnosis that were

excluded to prevent including CRC-related comorbidities [14].

The study protocol was approved by the internal review board of the Andalusian School of Public Health (CP17/00206) and the ethics committee of the Department of Health of the Andalusian Regional Government (study 0072-N-18).

2.2. Variables related to patient characteristics

The main outcome of the study was short-term overall mortality at 6 months and 1 year after cancer diagnosis and the main exposure was multimorbidity. Age, sex, type of surgery, chemotherapy and cancer stage were also included in the study as confounders.

Age at diagnosis was categorised into <55, 55–64, 65–74 and ≥75 years. Comorbidities were classified based on the Royal College of Surgeons (RCS) score, a modified version of the Charlson's comorbidity score, which reduces the number of comorbidities to 12, removes a category (peptic ulcer disease) and groups diseases together (e.g. diabetes mellitus codes with or without complications are grouped into a single category). The score does not assign weights to individual comorbidities [15]. The final score simply counts the total number of comorbidities for each patient as no comorbidities, one comorbidity and two or more comorbidities, with two or more comorbidities defined as multimorbidity [15]. The type of surgery was categorised as no receiving surgery, minor and major surgery, based on the Classification of Interventions and Procedures (fourth version, 'OPCS-4') (Supplementary Table S2). Chemotherapy was categorized as neoadjuvant, adjuvant, palliative and not receiving it. The final cancer-stage variable was defined as the combination of clinical and pathological TNM stages and categorised into four groups based on the TNM manual, 7th edition (AJCC staging system).

2.3. Statistical analysis

We described the study population and computed the unadjusted mortality rates per 100 person-years and unadjusted mortality rate ratios with 95% confidence intervals (CIs). We estimated non-parametrically the cumulative incidence of death at 6 months and 1 year according to comorbidity status using the Nelson–Aalen estimator and log-rank test [16].

We used a flexible parametric modelling approach consisting of restricted cubic spline-based hazard models with three knots [17] to derive multivariable excess mortality hazard ratios (HRs) and 95% CIs for multimorbidity after adjusting for age at diagnosis, sex, cancer stage and treatment and using as reference the category at lower risk. Due to data sparsity, chemotherapy and type of surgery were dichotomized as yes, for patients receiving it, and no for those patients who did not receive it. To account for the non-proportionality effect of multimorbidity, we included the interaction between the restricted cubic splines of time and the multimorbidity variable. From the final full-adjusted model we then derived the cumulative incidences of death by comorbidity status (i.e. no comorbidities, one comorbidity and two or more comorbidities) that were standardised to the empirical distribution of age, sex, cancer stage and treatment [18,19].

Finally, we described the 10 most frequent patterns of multimorbidity, derived the adjusted excess mortality HRs comparing each multimorbidity pattern with no comorbidity or any other different pattern with respect to the total sample and plotted the 1-year cumulative incidence of death for each multimorbidity pattern adjusted for age, sex, cancer stage and treatment.

In sensitivity analysis, we restricted the analysis to only those patients with tumour stage I–III receiving surgery plus tumour stage IV patients, we tested the interaction between comorbidities with patients' age and tumour stage on cancer outcomes and estimated the linear multiplicative combined effect of multimorbidity with tumour stage and patients' age at 1 year after diagnosis.

We used Stata v.15.1 (StataCorp, College Station, Texas, U.S.) including the user-written programs *stpm2* v.1.7 and *stpm2_standsurv* v.1.1.1 for statistical analysis and provide the Stata code used to run the analysis as a supplementary file.

3. Results

Among the study participants, 1,048 cases were diagnosed with cancers of the colon and rectum, 2 cases with cancer of the anus with overlapping sites of the rectum and 11 cases with anal adenocarcinomas but treated as CRC patients. Among 1,061 CRC patients, 171 (16.1%) died before 6 months and 246 (23.2%) died before the 1-year follow-up. The overall mortality rates were 36.2/472.6 and 27.4/897.2 person-years at 6 months and 1 year, respectively. Table 1 shows the patients' vital status, age, sex, cancer stage, type of surgery and chemotherapy by comorbidity status. Older CRC patients (≥75 years) showed a higher multimorbidity prevalence than younger CRC patients (<55 years) (43.7% vs. 8.5%). Male CRC patients also showed a higher multimorbidity prevalence than female patients (34.0% vs. 27.0%). Furthermore, CRC patients who died before 1 year had approximately two times higher prevalence of multimorbidity than those who were alive at 1 year (45.2% vs. 27.0%) and at 6 months (49.1% vs. 27.8%). However, no significant association was found between comorbidity status and cancer stage. Patients who did not receive surgery and chemotherapy had approximately two times higher

Table 1
Vital status, age, sex, cancer stage and cancer treatment according to the comorbidity status among colorectal cancer patients in Spain in 2011 (n = 1,061, 171 deaths at 6 months and 246 deaths at 1 year).

Variable	No comorbidity	One comorbidity	Two or more: multimorbidity	p-value
	N (%)	N (%)	N (%)	
Vital status at 6 months				<0.001
Alive	377 (43.2%)	253 (29.0%)	243 (27.8%)	
Dead	36 (21.8%)	48 (29.1%)	81 (49.1%)	
Vital status at 1 year				<0.001
Alive	349 (43.7%)	234 (29.3%)	216 (27.0%)	
Dead	64 (26.8%)	67 (28.0%)	108 (45.2%)	
Age at diagnosis, years				<0.001
<55	94 (72.3%)	25 (19.2%)	11 (8.5%)	
55–64	118 (54.6%)	63 (29.2%)	35 (16.2%)	
65–74	94 (34.9%)	82 (30.5%)	93 (34.6%)	
≥75	107 (25.3%)	131 (31.0%)	185 (43.7%)	
Sex				0.019
Male	232 (37.0%)	183 (29.0%)	215 (34.0%)	
Female	181 (44.0%)	118 (29.0%)	109 (27.0%)	
TNM stage				0.163
I	74 (44.3%)	46 (27.5%)	47 (28.1%)	
II	92 (33.3%)	85 (30.8%)	99 (35.9%)	
III	115 (40.8%)	76 (27.2%)	89 (31.9%)	
IV	108 (40.7%)	85 (32.1%)	72 (27.2%)	
Type of surgery				0.004
No surgery	49 (28.7%)	49 (28.7%)	73 (42.6%)	
Minor surgery	21 (48.8%)	11 (25.6%)	11 (25.6%)	
Major surgery	331 (41.3%)	235 (29.3%)	235 (29.3%)	
Chemotherapy				<0.001
Neoadjuvant	64 (50.8%)	36 (28.6%)	26 (20.6%)	
Adjuvant	126 (47.9%)	79 (30.0%)	58 (22.0%)	
Palliative	43 (44.3%)	31 (32.0%)	23 (23.7%)	
Not received	176 (32.3%)	153 (28.1%)	215 (39.5%)	

Missing values: TNM stage, n(%) = 60(5.6%), comorbidities, n(%) = 23(2.2%), type of surgery, n(%) = 27(2.4%) and chemotherapy, n(%) = 22(2.0%).

prevalence of multimorbidity than those who received major surgery (i.e. 42.6% vs. 29.3%). Similarly, patients who did not receive chemotherapy had approximately two times higher prevalence of multimorbidity than those who received any other type of chemotherapy (i.e. 39.5% vs. 23.7%, 22.0% and 20.6% for palliative, adjuvant and neoadjuvant chemotherapy, respectively) (Table 1).

Table 2 shows the short-term overall mortality rates by age, sex, cancer stage, type of surgery, chemotherapy and comorbidity status. Compared with other age groups, older patients (≥75 years) showed the highest mortality rate. For instance, the 1-year mortality rate of CRC patients aged ≥75 years was 47.5/100 person-years, twice as high as that of patients aged 65–74 years (25.1/100 person-years).

CRC patients who did not receive surgery and those with stage IV disease showed the highest mortality rates with 127.1/100 and 74.4/100 person-years at 1 year, respectively. Overall, CRC patients with multimorbidity showed higher mortality rates at 6 months and 1 year than those with one comorbidity or none. The mortality rate ratios showed a higher risk for men, those who were diagnosed at an age of ≥75 years, those diagnosed at a stage IV, those non-treated and those with multimorbidity (Table 2).

Table 3 shows the adjusted excess mortality HRs for comorbidity and multimorbidity at 6 months and 1 year. Overall, CRC patients with multimorbidity had approximately two times higher excess short-term mortality risk than those without comorbidities (adjusted model 4, Table 3: HR at 6 months, 2.04; 95% CI, 1.30–3.32 and at 1 year, 1.54; 95% CI, 1.08–2.20), but after multivariable adjustment for age, sex, cancer stage and treatment, no significant association between one comorbidity and mortality at 1 year was found. Likewise, the ≥75-year group had higher excess mortality than the <55–64-year group only at 1 year after diagnosis (adjusted model 4, Table 3: HR at 6 months, 1.89; 95% CI, 0.83–4.27 and at 1 year, 1.88; 95% CI, 1.06–3.33), patients with stage IV CRC at diagnosis had thirteen times higher short-term excess mortality at 1 year than those with stage I (adjusted model 4, Table 3: HR, 13.20; 95% CI, 6.70–26.00). Non-treated patients (i.e. surgery or chemotherapy) had three and four times higher short-term mortality risk at 1 year than those

Table 2
Six-month (A) and one-year (B) mortality rates by sex, age, cancer stage, treatment and comorbidity status among colorectal cancer patients in Spain in 2011 (n = 1,061, 171 deaths at 6 months and 246 deaths at 1 year).

	Deaths per person-years	Mortality rate	Mortality rate ratio	95% CI	p-value
Six-month mortality (A)					
Sex					
Male	105/288.53	36.39	Ref.		
Female	66/184.10	35.85	0.99	0.72–1.34	0.924
Age at diagnosis, years					
<55	5/63.34	7.89	Ref.		
55–64	9/106.64	8.44	1.07	0.35–3.19	0.900
65–74	43/123.56	34.80	4.41	1.75–11.13	<0.001
≥75	114/179.09	63.66	8.06	3.29–19.75	<0.001
TNM stage					
I	5/82.61	6.05	Ref.		
II	41/125.83	32.58	5.38	2.13–13.62	<0.001
III	22/135.69	16.21	2.68	1.01–7.07	0.038
IV	89/105.76	84.15	13.90	5.65–34.23	<0.001
Type of surgery					
No surgery	89/57.79	153.99	Ref.		
Minor surgery	3/20.79	14.42	0.09	0.03–0.30	<0.001
Major surgery	70/385.34	18.16	0.12	0.09–0.16	<0.001
Chemotherapy					
Neoadjuvant	4/62.05	6.45	Ref.		
Adjuvant	2/131.59	1.52	0.23	0.43–1.29	0.069
Palliative	19/44.65	42.55	6.60	2.25–19.40	<0.001
Not received	142/226.44	67.71	9.73	3.60–26.28	<0.001
Comorbidity status					
No comorbidity	36/195.17	18.45	Ref.		
One comorbidity	48/135.26	35.49	1.92	1.25–2.96	0.003
Multimorbidity	81/134.45	60.24	3.27	2.21–4.84	<0.001
One-year mortality (B)					
Sex					
Male	157/545.02	28.81	Ref.		
Female	89/352.16	25.27	0.97	0.68–1.14	0.324
Age at diagnosis, years					
<55	13/124.23	10.46	Ref.		
55–64	18/209.57	8.59	0.82	0.40–1.68	0.587
65–74	59/234.76	25.13	2.40	1.32–4.38	0.003
≥75	156/328.61	47.47	4.54	2.58–7.99	<0.001
TNM stage					
I	11/162.57	6.77	Ref.		
II	46/244.73	18.80	2.78	1.44–5.36	0.002
III	32/264.87	12.08	1.79	0.90–3.54	0.093
IV	136/182.88	74.37	15.5	5.95–20.32	<0.001
Type of surgery					
No surgery	118/92.86	127.07	Ref.		
Minor surgery	5/40.46	12.36	0.10	0.04–0.24	<0.001
Major surgery	108/749.62	14.41	0.11	0.09–0.15	<0.001
Chemotherapy					
Neoadjuvant	12/120.68	9.94	Ref.		
Adjuvant	15/259.99	5.77	0.58	0.27–1.24	0.155
Palliative	39/78.45	49.72	5.00	2.62–9.55	<0.001
Not received	175/423.29	41.34	4.16	2.32–7.46	<0.001
Comorbidity status					
No comorbidity	64/376.42	17.00	Ref.		
One comorbidity	67/257.32	26.04	1.53	1.08–2.16	0.014
Multimorbidity	108/249.34	43.31	2.55	1.87–3.47	<0.001

CI: confidence interval.
Missing values: TNM stage, n(%) = 60(5.6%), comorbidities, n(%) = 23(2.2%), type of surgery, n(%) = 27(2.4%) and chemotherapy, n(%) = 22(2.0%).

who did receive it (adjusted model 4, Table 3: HR at 1 year for no receiving surgery, 3.10; 95% CI, 2.14–4.48 and, 4.53; 95% CI, 3.13–6.54 for those patients who did not receive chemotherapy). However, no significant association was found between short-term mortality and sex.

Table 3
Short-term excess mortality hazard ratios for comorbidity and multimorbidity adjusted for sex, age, cancer stage and treatment among colorectal cancer patients in Spain in 2011 (n = 1,061, **171** deaths at 6 months and **246** deaths at 1 year).

Variable	Deaths (%)		Model 1 HR (95% CI)		Model 2 HR (95% CI)		Model 3 HR (95% CI)		Model 4 HR (95% CI)	
	6 m	1yr	6 m	1yr	6 m	1yr	6 m	1yr	6 m	1yr
Comorbidity status										
No comorbidity	3 (8.7)	64 (15.5)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
One comorbidity	48 (16.0)	67 (22.3)	1.42 (0.92 −2.21)	1.20 (0.84 −1.70)	1.38 (0.88 −2.19)	1.13 (0.79 −1.62)	1.58 (0.98 −2.56)	1.17 (0.81 −1.72)	1.69 (1.05 −2.72)	1.23 (0.84 −1.79)
Multimorbidity	81 (25.0)	108 (33.3)	2.00 (1.33 −3.01)	1.68 (1.21 −2.34)	2.27 (1.48 −3.48)	1.83 (1.30 −2.58)	2.13 (1.35 −3.35)	1.70 (1.19 −2.44)	2.04 (1.30 −3.20)	1.54 (1.08 −2.20)
Sex										
Male	105 (16.3)	157 (24.4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female	66 (15.9)	89 (21.5)	1.06 (0.78 −1.46)	0.93 (0.71 −1.21)	1.18 (0.85 −1.63)	1.02 (0.78 −1.35)	1.09 (0.78 −1.53)	0.99 (0.75 −1.32)	1.08 (0.78 −1.52)	0.97 (0.73 −1.29)
Age at diagnosis										
<55	5 (3.9)	13 (10.0)	1.01 (0.33 −3.02)	1.27 (0.62 −2.60)	1.04 (0.34 −3.19)	1.22 (0.59 −2.52)	0.88 (0.23 −3.43)	1.18 (0.53 −2.62)	0.78 (0.20 −3.06)	1.07 (0.48 −2.38)
55–64	9 (4.1)	18 (8.2)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
65–74	43 (15.8)	59 (21.7)	3.43 (1.66 −7.08)	2.54 (1.49 −4.32)	3.52 (1.64 −7.55)	2.62 (1.52 −4.52)	4.49 (2.00 −10.09)	3.09 (1.76 −5.43)	2.79 (1.23 −6.34)	2.38 (1.34 −4.20)
≥75	114 (26.1)	156 (35.8)	5.79 (2.90 −11.54)	4.50 (2.73 −7.40)	5.74 (2.76 −11.94)	4.59 (2.74 −7.70)	5.15 (2.35 −11.28)	3.91 (2.28 −6.68)	1.89 (0.83 −4.27)	1.88 (1.06 −3.33)
TNM stage										
I	5 (3.0)	11 (6.5)			Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
II	41 (14.6)	46 (16.4)			4.02 (1.58 −10.19)	2.15 (1.11 −4.17)	4.13 (1.62 −10.52)	2.24 (1.15 −4.34)	5.18 (2.03 −13.21)	2.76 (1.42 −5.37)
III	22 (7.7)	32 (11.2)			2.32 (0.87 −6.20)	1.59 (0.80 −3.17)	2.61 (0.98 −6.98)	1.72 (0.86 −3.46)	5.62 (2.08 −15.18)	3.41 (1.68 −6.94)
IV	89 (33.3)	136 (50.9)			13.16 (5.34 −32.43)	10.43 (5.63 −19.32)	6.11 (2.40 −15.51)	5.65 (2.97 −10.75)	15.14 (5.77 −39.70)	13.20 (6.70 −26.00)
Surgery										
Yes	73 (8.5)	113 (13.2)					Ref.	Ref.	Ref.	Ref.
No	89 (50.9)	118 (67.4)					4.41 (2.88 −6.75)	3.65 (2.57 −5.18)	3.52 (2.23 −5.57)	3.10 (2.14 −4.48)
Chemotherapy										
Yes	25 (5.1)	66 (13.6)							Ref.	Ref.
No	142 (25.7)	175 (31.7)							7.62 (4.62 −12.58)	4.53 (3.13 −6.54)

HR, hazard ratio; **CI**, confidence interval.
Model 1, adjusted for sex and age; **Model 2**, adjusted for sex, age and TNM stage; **Model 3**, adjusted for sex, age, TNM stage and type of surgery; **Model 4**, adjusted for sex, age, TNM stage, type of surgery and chemotherapy. **Missing values**: TNM stage, n(%) = 60(5.6%), comorbidities, n(%) = 23(2.2%), type of surgery, n(%) = 27(2.4%) and chemotherapy, n(%) = 22(2.0%).

Fig. 1 shows the unadjusted cumulative incidences of death at 6 months and 1 year by comorbidity status. CRC patients with multimorbidity showed a consistently higher cumulative incidence of death at 6 months and 1 year after cancer diagnosis than those with no comorbidity (log-rank test $p < 0.001$) (Fig. 1). Furthermore, we found a significant increasing trend of cumulative incidence by comorbidity status (test for trend $p < 0.001$).

Fig. 2 shows the cumulative incidences of death standardised to the empirical distribution of age, sex and cancer stage. CRC patients with multimorbidity had a consistently higher cumulative incidence than those with one or no comorbidities at 6 months and 1 year. The differences were markedly higher at 6 months than at 1 year, and there was no significant difference in cumulative incidence between those with one comorbidity and those without comorbidities at either 6 months or 1 year (Fig. 2).

Supplementary Table S3 shows the multimorbidity prevalence and 10 most frequent multimorbidity patterns. A total of 324 patients (31.2%) had multimorbidity. The most frequent pattern was congestive heart failure (CHF) + diabetes (5.8%), followed by CHF + chronic obstructive pulmonary disease (COPD) (4.2%) and peripheral vascular disease + diabetes

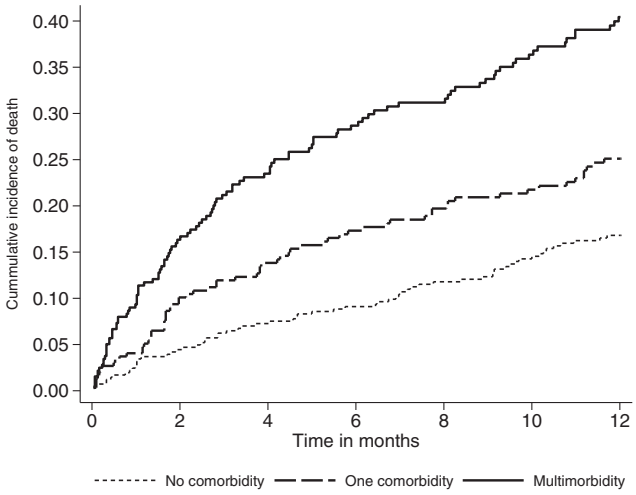

Fig. 1. Unadjusted short-term cumulative incidences of death by comorbidity status among colorectal cancer patients in Spain in 2011 (n = 1,061, 171 deaths at 6 months and 246 deaths at 1 year).

(4.1%). There was no evidence of an increase mortality risk at 1 year for any of the top 10 most frequent multimorbidity patterns except for only those patients with CHF and rheumatologic disease in combination with diabetes. For instance, patients with CHF + diabetes had approximately two times excess mortality risk than patients with no comorbidities or any other different comorbidity pattern (HR, 1.68; 95% CI: 1.07–2.65) and those with rheumatologic disease plus diabetes had two times excess mortality risk (HR, 2.23; 95% CI: 1.23–4.07). Supplementary Fig. S1 shows the cumulative incidences of death for the 10 most frequent multimorbidity patterns.

In sensitivity analysis, the excess mortality HR for the fully adjusted model 4 restricted to stage I–III patients receiving surgery plus all stage IV patients was consistent with the unrestricted model but a slight reduction in the strength of the association was observed (i.e. comorbidity

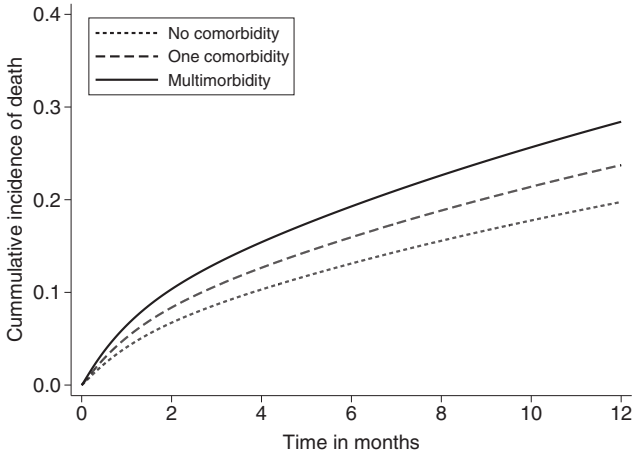

Fig. 2. Short-term cumulative incidences of death by comorbidity status, adjusted for age, sex, cancer stage and treatment, among colorectal cancer patients in Spain in 2011 (n = 1,061, 171 deaths at 6 months and 246 deaths at 1 year).

HR for the unrestricted model = 1.23, 95% CI: 0.84–1.79 vs. 1.21, 95% CI: 0.82–1.78 for the unrestricted, and multimorbidity HR for the unrestricted = 1.54, 95% CI: 1.08–2.20 vs. 1.43, 95% CI: 1.00–2.07 for the restricted model). Furthermore, there was evidence of an interaction between comorbidities with patients' age and tumour stage. Table 4 shows the stratum-specific adjusted HRs for comorbidities and multimorbidity by cancer stage (I–II, III and IV) and the combined linear multiplicative effect of comorbidities with cancer stage and patient's age. The association of comorbidities and multimorbidity was stronger in early-stage tumours (I–II), and there was evidence of a higher risk of short-term mortality at 1 year for only patients with multimorbidity at stages I–II (i.e. stratum-specific HR = 3.83, 95% CI:1.58–9.28) (Table 4A). The combined linear multiplicative effect of comorbidities and cancer stage showed that patients with both multimorbidity and tumour stage IV had ten times higher excess mortality risk than those patients without comorbidity and tumour stage I–II. Furthermore, CRC patients with multimorbidity and aged ≥70 years showed three times higher excess mortality risk than those patients without comorbidity and tumour stage I–II (Table 4B).

4. Discussion

We found that multimorbidity was a strong independent predictor of short-term mortality among CRC patients in Spain. However, after adjusting for age, sex, cancer stage at diagnosis and treatment, no significant association was found between increased short-term mortality at 1 year and having just one comorbidity. Our results are consistent with previous evidence showing that the impact of multimorbidity on short-term mortality is particularly strong in early-stage tumours and older patients [20] and the findings of a Japanese study with 2,007 participants [21]. They found that age and comorbidities worsened the overall survival of CRC patients who underwent curative surgery. However, patients aged ≥75 years were undertreated regardless of cancer stage despite the possibility of overall survival improvement by adjuvant therapy. Quintana *et al.* [22] found that a Charlson comorbidity index of ≥4 and an age of >75 years were predictors of 1-year mortality. More recently, a meta-analysis found that CRC patients with mild/moderate and severe comorbidities had a higher 30-day mortality risk than those without comorbidities (odds ratio, 1.7, 95% CI: 1.26–2.31) [23]. However, previous studies have not explored the impact of different multimorbidity patterns, and most of them based multimorbidity patterns on a non–cancer-specific comorbidity score.

We found that among patients with multimorbidity, diabetes was the most prevalent comorbidity. Diabetes has been shown as the most prevalent comorbidity among CRC patients [24]. A recent meta-analysis of

Table 4
Cancer stage stratum-specific adjusted short-term excess mortality hazard ratios (A) and multiplicative effect of multimorbidity/comorbidity with cancer stage and age on short-term mortality (1 year) (B) among colorectal cancer patients in Spain, 2011 (n = 970 and 246 deaths at 1 year).

A: Stratum-specific adjusted[a] HRs for cancer stage			
Comorbidity status	**Tumour stage**		
	TNM I-II N = 442	**TNM III N = 277**	**TNM IV N = 251**
	HR (95%CI)	HR (95%CI)	HR (95%CI)
No comorbidity	Ref.	Ref.	Ref.
One comorbidity	2.10 (0.79–5.55)	0.73 (0.25–2.19)	0.96 (0.60–1.51)
Multimorbidity	3.83 (1.58–9.28)	1.40 (0.55–3.58)	1.33 (0.85–2.10)
B: Comorbidity combined multiplicative adjusted[b] effects, n = 1,061			
Comorbidity status	**Tumour stage**		
	TNM I-II	**TNM III**	**TNM IV**
	HR (95%CI)	HR (95%CI)	HR (95%CI)
No comorbidity	Ref.	1.71 (1.07–2.74)	6.50 (4.27–9.90)
One comorbidity	1.24 (0.85–1.81)	2.13 (1.17–3.88)	8.09 (4.61–4.20)
Multimorbidity	1.63 (1.15–2.32)	2.80 (1.57–4.99)	10.63 (6.07–18.60)
	Age at diagnosis in years		
	<55	**55–69**	**≥70**
	HR (95%CI)	HR (95%CI)	HR (95%CI)
No comorbidity	Ref.	1.39 (0.69–2.80)	1.99 (1.01–3.92)
One comorbidity	1.25 (0.86–1.82)	1.74 (0.81–3.75)	2.49 (1.20–5.16)
Multimorbidity	1.67 (1.17–2.37)	2.33 (1.09–4.96)	3.33 (1.64–6.74)

Missing values: TNM stage, n(%) = 60(5.6%), comorbidities, n (%) = 23(2.2%), type of surgery, n(%) = 27(2.4%) and chemotherapy, n(%) = 22(2.0%).
[a] Adjusted for age, sex and cancer treatment.
[b] Adjusted for sex, cancer stage and treatment.

cohort studies found that patients with diabetes had a shorter 5-year overall survival than those without diabetes [25]. However, our findings are more specific as we found that it was not only diabetes that was responsible for the higher excess mortality risk among CRC patients but also the combination of diabetes with CHF and rheumatologic disease. Furthermore, our study shows a clear dose response effect of comorbidities on CRC short-term mortality.

Multimorbidity is highly prevalent among the elderly. Over 60% of cancer cases are diagnosed after 65 years of age, with 67% of cancer deaths occurring in this age group [26]. The elderly have less resistance and more prolonged exposure to carcinogens, a decline in immune functioning, an alteration in anti-tumour defence mechanisms, decreased DNA repair, defects in tumour-suppressor genes and differences in biological behaviour, including angiogenesis. These natural frailties and the increased prevalence of multimorbidity might detrimentally affect their treatment and survival outcomes [27]. The elderly are less likely to receive optimal cancer treatment [28].

Despite the high prevalence of multimorbidity among cancer patients, the guidelines and delivery of cancer care generally focus on single-disease management [29,30]. However, effective management of comorbid conditions is important in optimizing the patient's health status [31], and decisions regarding cancer treatment among the elderly cancer patients require careful consideration of comorbidities and multimorbidity [9,32,33]. Furthermore, postoperative complications occur more frequently in patients with comorbidities and multimorbidity [10,34], and certain comorbid conditions have been linked to adverse outcomes following surgery for cancer [9,35]. For instance, cancer patients with solid tumours and multimorbidity receiving surgery had a reduced immediate postoperative survival and an increased short-term mortality in the first 6 months after surgery [36]. Therefore, cancer research should address multimorbidity minimizing the occurrence of treatment-related complications.

Cancer control and treatment research should address multimorbidity, particularly in the elderly [37]. Considering the increased multimorbidity prevalence in older age groups and the poorer short-term survival in these age groups as shown in this study, healthcare professionals need to be vigilant for common comorbidities when providing medical care to patients because of the tendency toward poor tolerance to cancer treatment and occurrence of complications related to the interaction between age-related decline in physiological reserves and comorbidities [27]. Thus, improved coordination and communication between different healthcare disciplines are crucial to optimizing the

management of pre-existing comorbid conditions for the best cancer survival outcomes and minimizing the occurrence of treatment-related complications among the elderly.

Social inequalities also play a role in CRC survival. Fowler *et al.* analysed the socioeconomic status of 69,769 English patients and concluded that the probability of death rose with increasing deprivation, even after accounting for the main prognostic factors [38]. Our study design is limited in that it does not allow adjustment for socioeconomic status; thus, further research is necessary to explore the impact of socioeconomic status on short-term CRC survival in Spain. Moreover, including only one calendar year of CRC incident cases from only two population-based cancer registries might have limited the external validity of our findings. This restriction was due to data availability and the assessment of patients' follow-up. However, our findings are consistent with current evidence, and most importantly, they are unique and relevant for public health policy as to our knowledge, this is the first study to investigate the association between multimorbidity and short-term mortality among CRC patients in Spain. The treatment of CRC, especially for stage III and IV, influences the survival outcomes of CRC patients. For stage III patients, adjuvant treatment using chemotherapy is standard (unless very old and frail), and for stage IV, the treatment intent is most likely palliative, and mainstay of treatment is generally chemotherapy instead of surgery [39,40]. Thus, the inclusion of the treatment information in our study is a strength. However, in multivariate analysis given the small number of events we had to dichotomize both variables limiting the scope of the available information. Finally, we performed a complete case analysis given the reduced percentage of missing values (i.e. 2.2% for comorbidities) and caution is required in the interpretation of the unadjusted and adjusted HRs due to small numbers, particularly for some categories of age and cancer stage and the stratum specific HRs in the sensitivity analysis.

The most commonly used comorbidity index in population-based cancer epidemiology is the Charlson's Comorbidity Index [41]. However, controversies exist regarding the application of different comorbidity scores and their weighting algorithms. The CCI has been criticised for using weights that are not cancer specific [32], it includes some conditions that have not been shown to have an impact on survival among patients with cancer, and it assumes that the impact of multiple conditions is additive on a relative risk scale [42,43]. However, the RCS-modified Charlson score is a simple cancer-specific multimorbidity indicator that shifts the focus from a single disease paradigm to one where the causes and effects of multiple combined conditions are explored. Using the RCS-modified Charlson comorbidity score, originally used to evaluate mortality risk during surgery, is another strength of this study. The score uses 12 comorbidities considered equally important and identified among CRC patients [15] and is thus cancer specific. Various other scoring systems for measuring comorbidity are not cancer-specific or focus only on single comorbid conditions in isolation [41,44,45]. However, there has been no agreed gold standard to measure comorbidity in cancer patients [46]. The validation of the RCS-modified Charlson score showed moderate to very good discrimination. There is evidence showing that the RCS-modified Charlson score improved the performance of predictive models for short-term outcomes (in-hospital mortality) as well as 1-year mortality (C-statistic: 0.87) [15]. CRC is a disease related with aging, and multimorbidity is often attributed to the aging process. Thus, the occurrence of multimorbidity is more realistically conceptualised using a multimorbidity score. However, in comparison to comorbidity, the term 'multimorbidity' indicates that no single condition holds priority over any of the co-occurring conditions, and it might be a limitation. Therefore, we provided the information on the individual comorbidities integrating the most common multimorbidity patterns identified among CRC patients in our study [47].

Tailored risk-assessment tools that consider the effects of multimorbidity and its treatment are needed to support clinicians when evaluating the possibility of multimorbidity in cancer patients. Currently, available tools for this purpose are based on generic algorithms [48], although approaches that are more sophisticated could take advantage of emerging technologies such as artificial intelligence [48].

In conclusion, we found that multimorbidity was a strong independent predictor of increased short-term excess mortality risk at 6 months and 1 year among CRC patients in Spain, and the most commonly identified multimorbidity patterns showed an excess short-term mortality risk. Our findings might help identify patients at a higher risk for poorer cancer and treatment outcomes. Early detection and risk-reduction strategies may reduce the adverse impact of some of these adverse effects on patients.

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Conflict of interest statement

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.01.021.

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