Title

The pattern of Comorbidities and Associated Risk Factors among Colorectal Cancer Patients in Spain: CoMCoR study.

Miguel Angel Luque-Fernandez[1,2,3*], Daniel Redondo-Sánchez[1,3], Miguel Rodríguez-Barranco[3,4], Mª Carmen Carmona-García[5,6,8], Rafael Marcos-Gragera[3,5,6,7], María José Sánchez[1,3,4]

[1] Non□Communicable Disease and Cancer Epidemiology Group, Biomedical Research Institute of Granada, University of Granada.
[2] Non-Communicable Disease Epidemiology. London School of Hygiene and Tropical Medicine. London, U.K.
[3] Biomedical Network Research Centers of Epidemiology and Public Health (CIBERESP), Madrid, Spain
[4] Andalusian School of Public Health, Granada, Spain
[5] Catalan Institute of Oncology, Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology, Girona, Spain.
[6] Descriptive Epidemiology, Genetics and Cancer Prevention Group, Biomedical Research Institute (IDIBGI), Girona, Spain.
[7] Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, Girona, Spain.
[8] Department of Medical Oncology, Institut Català d'Oncologia Hospital Universitari de Girona Dr Josep Trueta, Girona, Spain.

* Corresponding author
E-mail: miguel.luque.easp@juntadeandalucia.es (MALF)

Abstract

Colorectal cancer is the second most frequently diagnosed cancer in Spain. Cancer treatment and outcomes can be influenced by tumor characteristics, patient general health status and comorbidities. Numerous studies have analyzed the influence of comorbidity on cancer outcomes, but limited information is available regarding the frequency and distribution of comorbidities in colorectal cancer patients, particularly elderly ones, in the Spanish population. We developed a population-based high-resolution cohort study of all incident colorectal cancer cases diagnosed in Spain in 2011 to describe the frequency and distribution of comorbidities, as well as tumor and healthcare factors. We then characterized risk factors associated with the most prevalent comorbidities, as well as dementia and multimorbidity, and developed an interactive web application to visualize our findings. The most common comorbidities were diabetes (23.6%), chronic obstructive pulmonary disease (17.2%), and congestive heart failure (14.5%). Dementia was the most common comorbidity among patients aged ≥75 years. Patients with dementia had a 30% higher prevalence of being diagnosed at stage IV and the highest prevalence of emergency hospital admission after colorectal cancer diagnosis (33%). Colorectal cancer patients with dementia were nearly three times more likely to not be offered surgical treatment. Age ≥75 years, obesity, male sex, being a current smoker, having surgery more than 60 days after cancer diagnosis, and not being offered surgical treatment were associated with a higher risk of multimorbidity. Patients with multimorbidity aged ≥75 years showed a higher prevalence of hospital emergency admission followed by surgery the same day of the admission (37%). We found a consistent pattern in the distribution and frequency of comorbidities and multimorbidity among colorectal cancer patients. The high frequency of stage IV diagnosis among patients with

dementia and the high proportion of older patients not being offered surgical treatment are significant findings that require policy actions.

Introduction

Cancer accounted for 9.6 million deaths globally in 2018, and was the second most common cause of death in the world [1]. Colorectal cancer (CRC) is the most frequently diagnosed cancer in Spain, with 37,172 newly diagnosed cases in 2018 [2]. Despite the high prevalence of CRC in the elderly, the inclusion of this cohort in clinical trials is disproportionately low [3]. In addition to clinical and pathological characteristics of the tumor, general health status and comorbidities of patients also influence cancer treatment and outcomes. Comorbidity describes the existence of a long-term health condition or disorder in the presence of a primary disease of interest, such as cancer [4], whereas multimorbidity refers to the existence of more than one comorbid condition [5]. Comorbidity and multimorbidity are increasingly seen as a problem of the elderly, but have also been reported as occurring more often and at a younger age in patients of lower socioeconomic status [6, 7]. The presence of comorbidities can influence treatment options, and therefore should be thoroughly evaluated when studying prognosis, outcomes, and mortality in cancer patients. Despite the coexistence of health conditions being commonplace, the guidelines and delivery of care appear to be focused on single disease management [8, 9]. However, effective management of comorbid conditions is important in maintaining patients' optimal health status, as the presence of one could contribute to the development of another [10], and decisions regarding cancer treatment require the consideration of patients' comorbidities [11, 12]. Furthermore, post-operative complications

have been reported as higher in patients with comorbidity [13], and certain comorbid conditions have been linked to adverse outcomes following surgery for cancer [14].

As noted above, there is consistent evidence on the influence of comorbidities on cancer outcomes, but little is known about them in CRC patients. Thus, we aimed to describe the frequency and distribution of comorbidities and multimorbidity, as well as their associated risk factors in the cohort of all CRC incident cases diagnosed in Granada and Girona (Spain) in 2011.

Materials and methods

Study design, participants, data, and setting

We conducted a population-based cohort study including all CRC incident cases (C18-C21), according to the International Classification of Diseases for Oncology, 3rd Edition, (ICD-O-3), diagnosed in 2011 and followed up until December 31, 2016 from two population-based Spanish cancer registries (Girona and Granada). Data were obtained from hospital medical records following a detailed protocol from the European High Resolution studies collaboration (TRANSCAN-HIGHCARE project within ERA-Net) [15]. We recorded information regarding the cancer stage at diagnosis (TNM staging system, 7th edition), cancer diagnostic exams, tumor morphology, cancer treatment, patients' comorbidities, performance status, and vital status. All recorded comorbidities were extracted 6 months before the index cancer was diagnosed, based on a standardized protocol published elsewhere [16]. All information was classified as either patient, tumor, or healthcare factors. Our study proposal (CP17/00206) was titled “Comorbidities and Associated Risk Factors among Colorectal Cancer Patients in Spain” (CoMCoR), and

approved by an internal review board and an ethical review committee with internal number 0072-N-18.

Variables related to the patient's characteristics

We recorded patient's age, sex, smoking status, body mass index (BMI), performance status, comorbidities, and multimorbidity. Age at diagnosis was categorized into four age groups: <55, 55-64, 65-74, and ≥75 years. Smoking status was categorized as current, previous, and never smoker. BMI was categorized as normal (<25.0 kg/m^2), overweight (≥25.0 kg/m^2 and <30 kg/m^2), and obese (≥30 kg/m^2). Patients' performance status was ascertained using the Eastern Cooperative Oncology Group (ECOG) scale and categorized as normal (0); restricted but able to carry out light work (1); restricted, unable to work but capable of self-care (2); restricted, capable of limited self-care (3); and disabled (4) [17]. Comorbidities were classified based on the Royal College of Surgeons modified Charlson score that reduces the number of comorbidities to 12 (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), rheumatic disease, liver disease, diabetes mellitus, hemiplegia/paraplegia, renal disease and AIDS/HIV), removing some categories such as peptic ulcer disease (since it is not considered a chronic disease anymore), and grouping diseases together (e.g., diabetes mellitus codes with or without complications are grouped into one category). Furthermore, the score drops the weighting of comorbidities, and instead categorizes the number of comorbidities in three categories: 0, 1, and ≥2 as a multimorbidity indicator [18].

Variables related to tumor characteristics

We recorded the tumor topography, morphology, grade of differentiation, and stage at diagnosis. The final stage variable was defined as the combination of clinical and pathological TNM stages and categorized into five groups, based on the 7th edition of the TNM manual. Topography, grade of differentiation, and morphology were coded according to ICD-O-3.

Variables related to healthcare provision factors

We recorded the type of hospital admission, surgery, type of surgery, and time to surgery. Type of hospital admission indicated whether cancer patients had an emergency or planned admission. The type of surgery was dichotomized as major or minor, and the time to surgery was noted as the number of days from the date of cancer diagnosis to the date patients had the surgical intervention and categorized into five groups (0, 1 to <14, 14 to 30, 31 to 59 and ≥60 days). Emergency surgery was defined as surgery offered on the same day of an emergency hospital admission.

Statistical analysis

First, we calculated the prevalence of each of the 12 different comorbidities for the cohort of CRC patients. Then, we calculated the frequency and distribution of comorbidities by patient, tumor and healthcare factors using counts and proportions. The Chi-square, Fisher's exact, and score tests were used for statistical inference. We assumed missing data, in a completely at random pattern, and thus performed a complete case analysis. Afterward, we computed unadjusted, sex-adjusted, and age-adjusted comorbidity prevalence ratios (PRs) with 95% confidence intervals (CIs) by patient, tumor, and healthcare factors. Generalized linear models

with Poisson distribution and log link were fitted for the five most common comorbidities plus dementia. We included the specific comorbidity indicator as the dependent variable; patient, tumor, and health care factors were the independent variables [19]. To describe the risk factors associated with the presence of multimorbidity (≥2 chronic conditions vs. non-comorbidities) we fitted a multinomial logistic regression model using the Royal College of Surgeons modified Charlson score as the dependent variable, with patient, tumor, and health care factors as independent variables. Risk factors associated with multimorbidity were evaluated using non-comorbidity as the reference category. Then, we derived unadjusted, age-adjusted, and sex-adjusted risk ratios (ARRs) with 95% CIs. Finally, we developed an open source web application using advanced visualization tools (radar plots, heat maps and forest plots) [20] to reduce the dimensionality of the data and display the results for the ten most common comorbidities plus dementia, available at http://watzilei.com/shiny/CoMCoR/. Furthermore, we created a GitHub repository where the code used to develop the analysis and the web application can be accessed for reproducibility (https://github.com/migariane/CoMCoR).

Results

Patient and tumor characteristics

Table 1 shows the distribution of patient, tumor, and healthcare characteristics from the cohort of colorectal cancer patients under study. More than half (59%) of colorectal cancer patients had one or more comorbidities 6 months before cancer diagnosis, and 30% had multimorbidity. Men represented 61% of the cohort, 67% of patients were age >65 years, 12% had a restricted performance status, slightly more than half of them were previous or current

smokers (52%), and 49% were overweight or obese. The prevalence of the different tumor locations was 34% in the right colon, 32% in the left colon, and 33% in the rectum. The differentiation of the tumor was mostly grade two (56%); however, 19% of the tumors were not graded. Only 16% of colorectal cancer patients had a stage I tumor at diagnosis, while more than 50% of the cases were identified as stage III/IV. Six percent of patients had missing stage information. The type of hospital admission was principally planned (65%), and almost one out of five patients were admitted after visiting the hospital emergency department. Surgery was performed in 83% of the patients, and the most frequent type of surgery was major surgery (77%). The time to surgery exceeded 60 days for 26% of the patients. Sixteen percent of the colorectal cancer cases had emergency surgery (Table 1).

Table 1. Distribution of patient, tumor and healthcare characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Patient's characteristics	N(%)	**Healthcare factors**	N(%)	**Tumor's characteristics**	N(%)	**Comorbidities***	N(%)
Age in years		**Type hospital admission**		**Anatomical subsite**		**Multimorbidity Prevalence**	
<55	130(12.3)	Emergency	183(17.2)	Right colon	357(33.6)	None	413(38.9)
55 - 64	219(20.6)	Planned	693(65.3)	Left colon	340(32.1)	One	301(28.4)
65 - 74	272(25.6)	Missing	185(17.4)	Colon Unspecified	11(1.0)	Two	190(17.9)
≥75	440(41.5)	**Surgery**		Rectal	353(33.3)	Three	89(8.4)
Sex		Done	879(82.8)	**Grade of differentiation**		Four	30(2.8)
Male	644(60.7)	Not done	175(16.5)	One	168(15.8)	Five	11(1.0)
Female	417(39.3)	Missing	7(0.7)	Two	596(56.2)	Six	4(0.4)
Performance status ECOG score		**Type of Surgery**		Three	90(8.5)	Missing	23(2.2)
Normal (0)	259(24.4)	Not done	175(16.5)	Four	7(0.6)		
Restricted but able to carry out light work (1)	423(39.9)	Major	816(76.9)	Missing	200(18.9)		
Restricted, unable to work but capable of selfcare (2)	83(7.8)	Minor	43(4.1)	**Stage TNM**			
Restricted, capable of limited selfcare (3)	35(3.3)	Done but uknown type	20(1.9)	I	168(15.8)		
Disabled (4)	6(0.6)	Missing	7(0.7)	II	281(26.5)		
Missing	255(24.0)	**Time to surgery in months**		III	285(26.9)		
Smoking status		Emergency 0 days	171 (16.1)	IV	267(25.2)		
Current	130(12.3)	1 to <14 days	115(10.8)	Missing	60(5.6)		
Previous	298(28.1)	14 to 30 days	124(11.7)				
Never	505(47.6)	31 to 59 days	188(17.7)				
Missing	127(12.0)	60 and more days	280(26.4)				
BMI in kg/m2		Missing	8 (0.8)				
<25	226(21.3)	No surgery	175 (16.5)				
25.0 - 29.9	327(30.8)						
≥30	193(18.2)						
Missing	315(29.7)						

* Comorbidity score based on: Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. The British journal of surgery. 2010 May;97(5):772-81.

Supporting information Table S1 shows the prevalence of comorbidities among CRC patients at least 6 months before the cancer diagnosis, ordered by frequency. Diabetes mellitus, COPD, and congestive heart failure were the most common comorbidities among CRC patients (24%, 17%, and 15%, respectively). Figure 1 shows the distribution of the prevalence of the top-ten comorbidities by sex. The most common comorbidity among men was COPD and rheumatologic disease and dementia among women.

Figure 1. Radar plot displaying the prevalence of comorbidities by sex among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Figure 1 [here]

Figure 2 shows the distribution of the prevalence of the top-ten comorbidities by age. The most common comorbidity among elderly (age ≥75 years) was dementia and liver disease among patients aged <55 years.

Figure 2. Heat map displaying the prevalence of comorbidities by age among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Figure 2 [here]

Figure legend. Comorbidities: I Myocardial infarct; II Congestive heart failure; III Peripheral vascular disease; IV Cerebrovascular disease; V Dementia; VI Chronic pulmonary disease; VII Rheumatic disease; VIII Liver disease; IX Diabetes mellitus; XI Renal disease.

Table 2 shows the frequency and crude prevalence ratio of comorbidities for the five most common comorbidities plus dementia by tumor, patient, and health. Supporting information Table S2 shows sex-adjusted and age-adjusted comorbidity prevalence ratios by tumor, patient, and health care factors. The complete distribution of comorbidities is provided as supporting information (Supplementary Tables S3, S4, and S5).

Distribution and frequency of comorbidities by tumor characteristics

The pattern of comorbidities by sex shows a high prevalence of COPD among male colorectal cancer patients (79%), while almost 60% of patients with dementia or rheumatologic disease were female. There was a frequency gradient of comorbidities by age, with dementia (75%), congestive heart failure (64%), and renal disease (46%) as the most common comorbidities among the elderly. Patients' performance status varied among comorbidities as well. Ninety-two percent of liver disease patients and 80% of diabetes patients had ECOG performance score 0 or 1, in contrast to only 53% of dementia and 30% of congestive heart failure patients. There was strong evidence supporting a significant trend of comorbidity prevalence across the levels of performance status for the five most common comorbidities plus dementia. Furthermore, COPD, diabetes, and dementia were more frequently associated with smoking (current and previous): 68%, 53%, and 36%, respectively. Adjusted PRs (APRs) comparing current smoker vs. never smoker in COPD, diabetes, and dementia were 3.1 (95% CI: 1.9-5.0), 1.3 (95% CI: 0.8-2.0), and 1.8 (95% CI: 0.6-5.2), respectively. Overweight and obesity

were more prevalent among patients with congestive heart failure (81%), peripheral vascular disease (76%), and diabetes (77%). The respective comorbidity APRs comparing a BMI ≥30 kg/m^2 vs. <25 kg/m^2 were 2.1 (95% CI: 1.2-3.6) for congestive heart failure, 1.7 (95% CI: 1.0-2.7) for peripheral vascular disease, and 1.7 (95% CI: 1.2-2.4) for diabetes. However, patients with dementia showed the highest prevalence of underweight and normal weight (body mass index <25 kg/m^2) patients (41%) (Tables 2 and S2).

Distribution and frequency of comorbidities by tumor's characteristics

The most prevalent comorbidity in right colorectal cancer patients was dementia (44%) and rheumatic disease for rectal cancer patients (38%). Regarding the grade of differentiation, the most common grade for all the different comorbidities was grade two (moderately differentiated). However, diabetes had the highest proportion of grade three (30%) and an APR of 1.4 (95% CI: 0.9-2.0) comparing grades three-four vs. one. Overall, all comorbidities had approximately 55% of cancer cases diagnosed at stages III or IV. Patients with COPD showed the lowest frequency of stage IV (22%). CRC patients with dementia had a 30% higher prevalence of advanced cancer diagnosis i.e. APR 1.3; 95% CI: 0.5-3.2 comparing stage IV vs I (Tables 2 and S2).

Distribution and frequency of comorbidities by healthcare characteristics

Patients with dementia showed the highest prevalence of emergency hospital admission after CRC diagnosis (33%) with an APR comparing planned vs. emergency admission of 1.6 (95% CI: 1.1-2.2). Despite the emergency admission, dementia was the comorbidity with the

highest prevalence of patients who were not offered surgery as treatment (64%) with an APR of 2.1 (95% CI: 1.2-3.8). Note that patients with dementia also showed the second highest prevalence of stage IV, with 30% of the cases. However, patients with rheumatologic disease showed the highest prevalence of major surgery (91%) and also the highest APR for minor surgery (2.0; 95% CI: 1.0-3.7). Major surgery was the most common type of surgery among all CRC patients, with at least 90% for all comorbidities. The pattern of time to surgery by comorbidities showed considerable variability. Overall, among the majority of comorbidities, one-third of CRC patients were offered surgery 60 or more days after the cancer diagnosis. However, dementia patients showed a different pattern: 30% had emergency surgery the same day as hospital admission (time to surgery of zero days). CRC with congestive heart failure showed the highest APR (1.7; 95% CI: 1.0-2.9) comparing surgery more than 60 days vs. emergency surgery (zero days) (Tables 2 and S2).

Table 2. Distribution and frequency of the top five comorbidities plus dementia and associated risk ratios by patient, tumor and healthcare characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

		II			III			V			VI			VII			IX		
		n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value
Patient's factors	**Total**																		
Age in years				<0.001*			0.036*			<0.001*			<0.001*			0.006*			<0.001*
<55	130	4(2.6)	(Reference)		9(7.3)	(Reference)		2(4.2)	(Reference)		8(4.4)	(Reference)		6(5.8)	(Reference)		6(2.4)	(Reference)	
55 - 64	219	17(11)	2.5(0.9, 7.4)		22(17.7)	1.5(0.7, 3.1)		5(10.4)	1.5(0.3, 7.6)		21(11.5)	1.6(0.7, 3.4)		13(12.5)	1.3(0.5, 3.3)		42(16.8)	4.2(1.8, 9.6)	
65 - 74	272	34(22.1)	4.1(1.5, 11.3)		36(29.0)	1.9(1.0, 3.9)		5(10.4)	1.2(0.2, 6.1)		57(31.3)	3.4(1.7, 7.0)		30(28.8)	2.4(1.0, 5.7)		86(34.4)	6.9(3.1, 15.4)	
≥75	440	99(64.3)	7.6(2.8, 20.2)		57(46.0)	1.9(1.0, 3.8)		36(75.0)	5.5(1.3, 22.6)		96(52.7)	3.7(1.8, 7.3)		55(52.9)	2.8(1.2, 6.4)		116(46.4)	5.9(2.7, 13.1)	
Sex				0.635			0.870			0.014			<0.001			<0.001			0.004
Male	644	96(62.3)	(Reference)		76(61.3)	(Reference)		21(43.8)	(Reference)		143(78.6)	(Reference)		42(40.4)	(Reference)		171(68.4)	(Reference)	
Female	417	58(37.7)	0.9(0.7, 1.3)		48(38.7)	1.0(0.7, 1.4)		27(56.3)	2(1.1, 3.5)		39(21.4)	0.4(0.3, 0.6)		62(59.6)	2.3(1.6, 3.3)		79(31.6)	0.7(0.6, 0.9)	
Performance status				<0.001*			<0.001*			<0.001*			0.001*			0.062*			0.005*
Normal (0)	259	20(16.0)	(Reference)		12(12.6)	(Reference)		1(3.3)	(Reference)		25(17.9)	(Reference)		19(19.0)	(Reference)		45(22.3)	(Reference)	
Restricted but able to carry out light work (1)	423	68(54.4)	2.1(1.3, 3.3)		62(65.3)	3.2(1.7, 5.7)		13(43.3)	7.9(1.0, 60.4)		89(63.6)	2.2(1.4, 3.3)		66(66.0)	2.1(1.3, 3.4)		117(57.9)	1.6(1.2, 2.1)	
Restricted, unable to work but capable of selfcare (2)	83	21(16.8)	3.3(1.9, 5.8)		10(10.5)	2.6(1.2, 5.8)		8(26.7)	25.2(3.2, 198.3)		16(11.4)	2.0(1.1, 3.6)		9(9.0)	1.5(0.7, 3.2)		25(12.4)	1.7(1.1, 2.7)	
Restricted, capable of limited selfcare (3)	35	12(9.6)	4.4(2.4, 8.2)		9(9.5)	5.5(2.5, 12.2)		6(20.0)	44.2(5.5, 356.6)		8(5.7)	2.4(1.2, 4.8)		4(4.0)	1.6(0.6, 4.3)		14(6.9)	2.3(1.4, 3.7)	
Disabled (4)	6	4(3.2)	8.6(4.2, 17.4)		2(2.1)	7.2(2.0, 25.2)		2(6.7)	86.0(9.0, 82.4)		2(1.4)	3.4(1.0, 11.3)		2(2.0)	4.5(1.3, 15.2)		1(0.5)	1.0(0.2, 5.8)	
Smoking status	255			0.028			0.858			0.406			<0.001			0.001			0.023
Current	130	12(8.9)	0.7 (0.4, 1.3)		15(13.0)	0.9 (0.5, 1.6)		5(12.8)	0.8 (0.3, 2.0)		35(20.7)	2.5 (1.6, 3.9)		9(9.8)	0.5 (0.3, 1.0)		31(14.0)	1.2 (0.8, 1.7)	
Previous	298	55(40.7)	1.4 (1.0, 2.0)		35(30.4)	0.9 (0.6, 1.4)		9(23.1)	0.6 (0.3,1.3)		80(47.3)	2.5 (1.8, 3.5)		16(17.4)	0.4 (0.2, 0.7)		87(39.2)	1.4 (1.0, 1.9)	
Never	505	68(50.4)	(Reference)		65(56.5)	(Reference)		25(64.1)	(Reference)		54(32.0)	(Reference)		67(72.8)	(Reference)		104(46.8)	(Reference)	
BMI in kg/m2				0.010*			0.038*			0.337*			0.057*			0.733*			0.001*
<25	226	17(19.5)	(Reference)		23(23.5)	(Reference)		12(41.4)	(Reference)		40(30.8)	(Reference)		22(32.4)	(Reference)		40(23)	(Reference)	
25.0 - 29.9	327	40(46.0)	1.6(0.9, 2.8)		42(42.9)	1.3(0.8, 2.0)		10(34.5)	0.6(0.3, 1.3)		41(31.5)	0.7(0.5, 1.1)		25(36.8)	0.8(0.5, 1.4)		74(42.5)	1.3(0.9, 1.8)	
≥30	193	30(34.5)	2.1(1.2, 3.6)		33(33.7)	1.7(1.0, 2.8)		7(24.1)	0.7(0.3, 1.7)		49(37.7)	1.4(1.0, 2.1)		21(30.9)	1.1(0.6, 2.0)		60(34.5)	1.8(1.2, 2.5)	

*****Score test for trend. **Comorbidities:** II Congestive heart failure; III Peripheral vascular disease; V Dementia; VI Chronic pulmonary disease; VII Rheumatic disease; IX Diabetes mellitus

		II			III			V			VI			VII			IX		
		n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value	n(%)	PR(95%CI)	P-value
Tumor factors	**Total**																		
Anatomical Site				0.63			0.913			0.360			0.390			0.742			0.195
Right colon	357	55(35.7)	(Reference)		44(35.5)	(Reference)		21(43.8)	(Reference)		67(36.8)	(Reference)		31(29.8)	(Reference)		98(39.2)	(Reference)	
Left colon	340	50(32.5)	1(0.7, 1.4)		41(33.1)	1.0(0.7, 1.5)		11(22.9)	0.5(0.3, 1.1)		63(34.6)	1.0(0.7, 1.3)		33(31.7)	1.1(0.7, 1.8)		74(29.6)	0.8(0.6, 1.0)	
Colon Unspecified	11	2(1.3)	1.8(0.6, 6)		1(0.8)	1.1(0.2, 7.1)		0(0)	,		1(0.5)	0.7(0.1, 4.7)		1(1.0)	1.6(0.3, 10.2)		2(0.8)	1.0(0.3, 3.3)	
Rectal	353	47(30.5)	0.9(0.6, 1.2)		38(30.6)	0.9(0.6, 1.3)		16(33.3)	0.8(0.4, 1.4)		51(28.0)	0.8(0.6, 1.1)		39(37.5)	1.3(0.8, 2.0)		76(30.4)	0.8(0.6, 1.0)	
Grade				0.834*			0.387*			0.430*			0.753*			0.414*			0.187*
I	168	24(19.8)	(Reference)		19(18.4)	(Reference)		3(9.1)	(Reference)		21(14.1)	(Reference)		19(22.6)	(Reference)		36(17.6)	(Reference)	
II	596	83(68.6)	0.9(0.6, 1.4)		77(74.8)	1.1(0.7, 1.7)		27(81.8)	2.4(0.7, 7.8)		116(77.9)	1.5(1, 2.3)		56(66.7)	0.8(0.5, 1.3)		138(67.6)	1.0(0.7, 1.4)	
III	90	13(10.7)	1.0(0.5, 1.8)		7(6.8)	0.7(0.3, 1.5)		2(6.1)	1.2(0.2, 7.0)		12(8.1)	1.0(0.5, 2.0)		8(9.5)	0.7(0.3, 1.6)		30(14.7)	1.5(1.0, 2.2)	
IV	7	1(0.8)	0.9(0.1, 6.0)		0(0)	-		1(3.0)	7.5(0.9, 63.5)		0(0)	-		1(1.2)	1.2(0.2, 7.7)		0(0)	-	
Stage				0.600*			0.372*			0.650*			0.621*			0.235			0.979*
I	168	25(16.9)	(Reference)		18(14.8)	(Reference)		6(14)	(Reference)		23(13.5)	(Reference)		17(16.5)	(Reference)		34(14.4)	(Reference)	
II	281	51(34.5)	1.2(0.8, 1.9)		31(25.4)	1.0(0.6, 1.8)		13(30.2)	1.3(0.5, 3.4)		57(33.3)	1.5(1.0, 2.3)		42(40.8)	1.5(0.9, 2.5)		69(29.2)	1.2(0.9, 1.8)	
III	285	29(19.6)	0.7(0.4, 1.1)		39(32.0)	1.3(0.8, 2.2)		11(25.6)	1.1(0.4, 2.9)		54(31.6)	1.4(0.9, 2.2)		16(15.5)	0.6(0.3, 1.1)		79(33.5)	1.4(1.0, 2.0)	
IV	267	43(29.1)	1.1(0.7, 1.7)		34(27.9)	1.2(0.7, 2.0)		13(30.2)	1.4(0.5, 3.5)		37(21.6)	1.0(0.6, 1.6)		28(27.2)	1.0(0.6, 1.8)		54(22.9)	1.0(0.7, 1.5)	
Healthcare factors	**Total**																		
Type hospital admission				0.685			0.686			0.084			0.405			0.259			0.015
Emergency	183	25(22.3)	(Reference)		19(19.2)	(Reference)		10(33.3)	(Reference)		34(23.3)	(Reference)		14(16.1)	(Reference)		30(14.7)	(Reference)	
Planned	693	87(77.7)	0.9(0.6, 1.4)		80(80.8)	1.1(0.7, 1.8)		20(66.7)	0.5(0.2, 1.1)		112(76.7)	0.9(0.6, 1.2)		73(83.9)	1.4(0.8, 2.4)		174(85.3)	1.5(1.1, 2.2)	
Surgery				<0.001			0.374			<0.001			0.288			0.732			0.865
Done	879	113(73.9)	(Reference)		100(80.6)	(Reference)		30(63.8)	(Reference)		147(80.8)	(Reference)		88(84.6)	(Reference)		206(83.1)	(Reference)	
Not done	175	40(26.1)	1.8(1.3, 2.5)		24(19.4)	1.2(0.8, 1.8)		17(36.2)	2.8(1.6, 5.0)		35(19.2)	1.2(0.9, 1.7)		16(15.4)	0.9(0.6, 1.5)		42(16.9)	1.0(0.8, 1.4)	
Type of Surgery				0.732			0.637			0.682			0.325			0.065			0.242
Major	816	108(95.6)	(Reference)		93(93.9)	(Reference)		28(96.6)	(Reference)		140(96.6)	(Reference)		79(90.8)	(Reference)		193(96.5)	(Reference)	
Minor	43	5(4.4)	0.9(0.4, 2.0)		6(6.1)	1.2(0.6, 2.6)		1(3.4)	0.7(0.1, 4.8)		5(3.4)	0.7(0.3, 1.5)		8(9.2)	1.9(1.0, 3.7)		7(3.5)	0.7(0.3, 1.3)	
Time to surgery in months				0.125*			0.027*			0.045*			0.181*			0.166*			0.018*
Emergency 0 days	171	16(14.3)	(Reference)		15(15.2)	(Reference)		9(30.0)	(Reference)		21(14.4)	(Reference)		11(12.6)	(Reference)		32(15.6)	(Reference)	
1 to <14 days	115	16(14.3)	1.5(0.8, 2.9)		10(10.1)	1.0(0.5, 2.1)		5(16.7)	0.8(0.3, 2.4)		19(13.0)	1.4(0.8, 2.4)		11(12.6)	1.5(0.7, 3.3)		18(8.8)	0.8(0.5, 1.4)	
14 to 30 days	124	13(11.6)	1.2(0.6, 2.3)		8(8.1)	0.8(0.3, 1.7)		4(13.3)	0.6(0.2, 2.0)		24(16.4)	1.6(1.0, 2.8)		11(12.6)	1.4(0.6, 3.2)		29(14.1)	1.3(0.8, 2.0)	
31 to 59 days	188	26(23.2)	1.5(0.8, 2.6)		28(28.3)	1.7(0.9, 3.0)		7(23.3)	0.7(0.3, 1.8)		32(21.9)	1.4(0.8, 2.3)		28(32.2)	2.3(1.2, 4.4)		56(27.3)	1.6(1.1, 2.3)	
60 and more days	280	41(36.6)	1.6(0.9, 2.7)		38(38.4)	1.6(0.9, 2.8)		5(16.7)	0.3(0.1, 1.0)		50(34.2)	1.5(0.9, 2.3)		26(29.9)	1.5(0.8, 2.9)		70(34.1)	1.3(0.9, 1.9)	

*Score test for trend. **Comorbidities**: II Congestive heart failure; III Peripheral vascular disease; V Dementia; VI Chronic pulmonary disease; VII Rheumatic disease; IX Diabetes mellitus

Table 3 shows the risk factors associated with the presence of multimorbidity versus the absence of comorbidities by patients, tumor, and healthcare factors. Overall, a higher risk of multimorbidity was associated with being aged ≥75 years, obese, male, or current smoker (Figure 3).

Figure 3. Forest plot: Multimorbidity risk factors by patients' age, sex, performance status and BMI among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Figure 3 [here]

Likewise, being offered surgery more than 60 days after cancer diagnosis and not being offered surgery were associated with a higher risk of multimorbidity. It is important to highlight that 37% of patients having emergency surgery had multimorbidity and were aged ≥75 years. Furthermore, 30% of emergency surgery was performed in older (≥75 years) advanced stage (III/IV) CRC patients affected by dementia. There was limited evidence supporting that patients with multimorbidity versus non-comorbidity had a 30% higher risk of not being offered surgery (RR 1.3; 95% CI: 0.9-2.1). However, we found strong evidence of surgery after 60 days in multimorbid CRC patients compared to patients with no comorbidity. Patients affected by multimorbidity had 2.4 times the risk of being offered late surgery compared to emergency surgery (0 days) (ARR: 2.4; 95% CI: 1.4-4.1) (Table 3).

Table 3. Multimorbidity risk factors by patient, tumor and healthcare characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Comorbidities distribution across levels of covariates			Multimorbidity vs. Non-comorbidity		
		n(%)	CRR(95%CI)	P-value	ARR(95%CI)
Patient's factors	**Total**				
Age in years				<0.001	
<55	130	11(8.5)	(Reference)		
55 - 64	216	35(16.2)	2.5 (1.2, 5.2)		
65 - 74	269	93(34.6)	8.4 (4.2, 16.8)		
≥75	423	185(43.7)	14.7 (7.6, 28.8)		
Sex				0.019	
Male	630	215(34.1)	(Reference)		
Female	408	109(26.7)	0.6 (0.4, 0.9)		
Performance status Ecog score				<0.001	
Normal (0)	257	40(15.6)	(Reference)		(Reference)
Restricted but able to carry out light work (1)	422	154(36.5)	4.6 (3.0, 7.0)		3.5 (2.2, 5.4)
Restricted, unable to work but capable of selfcare (2)	82	36(43.9)	6.8 (3.6, 12.8)		2.9 (1.4, 5.8)
Restricted, capable of limited selfcare or disabled (3, 4)	40	25(62.5)	24.7 (8.1, 75.0)		12.6 (3.9, 40.5)
Smoking status				0.006	
Current	130	40(30.8)	(Reference)		(Reference)
Previous	297	113(38.1)	1.4 (0.8, 2.3)		0.7 (0.4, 1.2)
Never	503	137(27.2)	0.7 (0.5, 1.1)		0.3 (0.2, 0.5)
BMI in kg/m2					
<25	226	57(25.2)	(Reference)	0.002	(Reference)
25.0 - 29.9	326	89(27.3)	1.0 (0.7, 1.5)		1.0 (0.6, 1.6)
≥30	193	79(40.9)	2.2 (1.4, 3.4)		2.4 (1.4, 4.0)
Tumor factors					
				0.414	
Right colon	348	118(33.9)	(Reference)		(Reference)
Left colon	335	104(31.0)	0.8 (0.6, 1.2)		0.9 (0.6, 1.2)
Colon Unspecified	7	3(42.9)	0.7 (0.5, 1.1)		0.8 (0.6, 1.2)
Rectal	348	99(28.5)	0.8 (0.2, 3.7)		1.0 (0.2, 5.8)
				0.821	
I	158	44(27.8)	(Reference)		(Reference)
II	592	189(31.9)	1.2 (0.8, 1.9)		1.0 (0.6, 1.5)
III-IV	96	27(28.1)	1.0 (0.5, 1.8)		0.7 (0.4, 1.4)
				0.163	
I	167	47(28.1)	(Reference)		(Reference)
II	276	99(35.9)	1.7 (1.0, 2.6)		1.2 (0.7, 1.9)
III	279	89(31.9)	1.2 (0.8, 1.9)		1.1 (0.7, 1.8)
IV	265	72(27.2)	1.0 (0.6, 1.7)		0.9 (0.5, 1.4)
Healthcare factors					
Type hospital admission				0.175	
Emergency	179	42(23.5)	0.7 (0.5, 1.1)		0.6 (0.4, 1.0)
Planned	682	206(30.2)	(Reference)		(Reference)
Surgery				<0.001	
Done	864	249(28.8)	(Reference)		(Reference)
Not done	171	73(42.7)	1.4 (0.9 2.2)		1.3 (0.9, 2.1)
Type of Surgery				0.623	
Major	801	235(29.3)	1.3 (0.6, 2,9)		1.0 (0.5, 2,4)
Minor	43	11(25.6)	(Reference)		(Reference)
Time to surgery in months				0.017	
Emergency 0 days	168	33(19.6)	(Reference)		(Reference)
1 to <14 days	111	26(23.4)	1.2 (0.6, 2.3)		1.2 (0.6, 2.4)
14 to 30 days	118	32(27.1)	1.4 (0.8, 2.5)		1.3 (0.7, 2.5)
31 to 59 days	188	60(31.9)	2.0 (1.2, 3.5)		2.1 (1.2, 3.7)
60 and more days	278	98(32.2)	2.0 (1.2, 3.3)		2.4 (1.4, 4.1)

CRR: Crude Risk Ratio; **ARR**: Adjusted Risk Ratio

Furthermore, the complete visualization of CoMCoR study results is provided at the following link http://watzilei.com/shiny/CoMCoR/.

Discussion

Overall, comorbidity is commonly recognized as being associated with cancer outcomes and survival [21]. However, there is an international sparsity of population-based epidemiological studies describing the prevalence of comorbidities and associated risk factors among cancer patients [22]. CoMCoR study fills this gap, providing translational evidence regarding the pattern of the prevalence of comorbidities, multimorbidity, and associated risk factors among CRC patients in Spain. The pattern is mainly characterized by a higher prevalence of diabetes, advanced cancer stage, and late surgery or no surgical treatment in older patients with dementia.

To the best of our knowledge, the CoMCoR study presented here is the first to identify the most prevalent comorbidities and associated risk factors among CRC patients in Spain, and characterize a particular pattern in the distribution and frequency of comorbidities and multimorbidity. While clinical studies are representative of only a selected part of the population, CoMCoR is a high-resolution population-based observational study using cancer registration and hospital medical records that translates its results into clinical practice based on real-world data.

Regarding the prevalence of comorbidities, we found that diabetes is the most prevalent comorbidity among CRC patients (24%). Among non-cancer populations, the prevalence of any

type of diabetes in adults in Spain has been reported to range between 6 and 11% [23]. However, there is a scarcity of literature reporting the prevalence of diabetes among CRC patients [22]. Our findings were similar to those previously reported in a Taiwanese cohort of 1,197 CRC patients where 24% had either a reported history of diabetes or were currently taking one or more diabetes-controlling medications [24]. Some evidence shows that diabetes is associated with higher incidence of CRC and shorter CRC survival [25]. Thus, we argue that public health programs targeting cancer prevention strategies among diabetic patients might have a positive impact on CRC outcomes in Spain.

Furthermore, we found a high prevalence of advanced stage cancer diagnosis (stage III/IV) among all CRC patients, which was even higher in older CRC patients affected by dementia. We argue that this may be due to low utilization of CRC screening in Spain. In 2011, CRC screening programs were implemented in only nine Spanish regions, with just partial coverage [26]. While all populations would benefit from the systematic use of screening, socioeconomically disadvantaged groups, such as patients with dementia, may also benefit from a targeted CRC screening [27].

Comorbid medical diseases are highly prevalent among elderly. Overall, over 60% of all cases of cancer are diagnosed after age 65 years, with 67% of cancer deaths occurring in this age group [28]. We found a high prevalence of older patients not being offered surgical treatment, but it was even higher for older patients with stage III/IV CRC and dementia. There are many reasons why cancer occurs more frequently in older persons. The elderly have less resistance and longer exposure to carcinogens, a decline in immune system functioning, an alteration in anti-

tumor defenses, decreased DNA repair, defects in tumor-suppressor genes, and differences in biological behavior, including angiogenesis. These factors contribute to the elderly population often being affected by comorbidities which affect cancer diagnosis, treatment, and survival [29]. The high prevalence we found of older CRC patients not being offered surgical treatment in stages III and IV partially it might reflect the low uptake and partial coverage of CRC screening and preventive strategies in Spain.

Regarding multimorbidity, we found that it is associated with late surgery (≥60 days after cancer diagnosis) and emergency surgery offered the same day of an emergency hospital admission. Recently published evidence has shown that CRC diagnosed after a hospital emergency room admission were more likely associated with older and more socioeconomically deprived individuals [30]. Although disease stage at the time of diagnosis of CRC is a crucial determinant of patient outcome, comorbidity increases the complexity of cancer management and affects survival duration. Cancer control and treatment research questions should address multimorbidity, particularly in the elderly [31]. Regarding the evidence examining time from cancer diagnosis to surgical treatment there is no conclusive evidence supporting an optimal window of time. However, a study from the American College of Surgeons has found that patients who had a cancer operation at precisely eight weeks (56 days) after the end of combined chemoradiotherapy had the best overall survival and successful removal of their residual tumors [32]. Other study found that CRC patients waiting longer than 12 weeks (84 days) to receive surgery had increased all-cause mortality compared with patients receiving surgery within four weeks (28 days) [33]. In a study of patients receiving elective surgery for colonic resection

following diagnosis with CRC in Ontario, it was found that factors influencing receipt of treatment after 42 days from diagnosis included older age and comorbidity [34].

Emergency surgery was defined as surgery offered the same day of an emergency hospital admission. Thus, we were assuming implicitly that CRC was diagnosed as a consequence of an emergency surgical intervention. However, we do not have empirical data to support our assumption. On the other hand, 30% of emergency surgery was performed among older advanced-stage CRC patients with dementia. It has been shown that CRC diagnosed after a hospital emergency admission is more likely associated with older and more deprived individuals [35, 36]. Recently, a study showed that 18% of CRC cases that were diagnosed as emergency cases had “red flag” symptoms, indicating the disease could have been identified earlier [30]. The promotion of CRC symptom awareness among the elderly might help them to early identify these symptoms and visit their general practitioner, who must refer them through the normal pathways to specialist evaluation [30].

There have been attempts to reanalyze the different comorbidity scores and their weighting algorithms, which show that some diseases should have a higher weight (including dementia), and others a lower weight (including peptic ulcers). Different approaches to measuring comorbidity specifically in cancer patients include focusing on single comorbid conditions in isolation, or weighted indices such as the Charlson comorbidity index [37], the Adult Comorbidity Evaluation – 27 index (ACE-27) [38], or the Elixhauser index [39]. However, to date, there is no agreed gold standard method upon which to measure comorbidity in the cancer patient population [40]. We used the Royal College of Surgeons system, which is a

clinical score used to evaluate the risk of death during surgery. The score applies an equal weight system to 12 different comorbidities categorized into 0, 1, 2 or more comorbidities, making it easy-to-use, since all comorbidities are considered equally important [18].

We assumed that missing data were completely at random and performed a complete case analysis, which might introduce bias if the data were actually missing at random. However, our CoMCoR study was merely descriptive, and the percentage of missing data for the main outcome (comorbidities) was only 2%. Also, we would like to acknowledge the limited scope of the analysis in terms of time and space, with only one calendar year of CRC incident cases and two population-based cancer registries, thus limiting the external validity of our findings and supporting the need of more studies.

In summary, the CoMCoR study has identified a consistent pattern in the distribution and frequency of comorbidities and multimorbidity for CRC patients in Spain, mostly associated with diabetes, dementia, advanced cancer diagnosis, older age, and surgical treatment. The high prevalence of CRC diagnosed at stage III/IV among elderly patients and patients with dementia and the high prevalence of older patients not being offered surgical treatment are significant findings that require immediate policy actions. Results from the CoMCoR study may help to foster CRC screening and preventive strategy policies in Spain and other countries.

Funding

MALF was supported for the Carlos III Institute of Health, Grant/Award Number: CP17/00206 and MJS for the Andalusian Department of Health, Grant Number: PI-0152/2017. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank Minicozzi Pamela and Sant Milena for the development of the protocol and data recollection tools for the European High-Resolution studies.

References

1. *World Health Organization. 2017. Cancer [Online]. Available:* http://www.who.int/cancer/en/ *[Accessed 30 October 2017].*
2. *Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from:* https://gco.iarc.fr/today*, accessed [14 January 2019].*
3. Shenoy, P. and A. Harugeri, *Elderly patients' participation in clinical trials.* Perspect Clin Res, 2015. **6**(4): p. 184-9.
4. Porta, M.S., et al., *A dictionary of epidemiology*. Sixth edition / ed. 2014, Oxford: Oxford University Press. xxxii, 343 pages.
5. Lujic, S., et al., *Multimorbidity in Australia: Comparing estimates derived using administrative data sources and survey data.* PLoS One, 2017. **12**(8): p. e0183817.
6. Macleod, U. and E. Mitchell, *Comorbidity in general practice.* Practitioner, 2005. **249**(1669): p. 282-4.

7. Macleod, U., et al., *Comorbidity and socioeconomic deprivation: an observational study of the prevalence of comorbidity in general practice.* Eur J Gen Pract, 2004. **10**(1): p. 24-6.

8. Tan, V., et al., *The triple whammy anxiety depression and osteoarthritis in long-term conditions.* BMC Fam Pract, 2015. **16**: p. 163.

9. Tinetti, M.E., T.R. Fried, and C.M. Boyd, *Designing health care for the most common chronic condition--multimorbidity.* JAMA, 2012. **307**(23): p. 2493-4.

10. McLean, G., et al., *The influence of socioeconomic deprivation on multimorbidity at different ages: a cross-sectional study.* Br J Gen Pract, 2014. **64**(624): p. e440-7.

11. Sarfati, D., B. Koczwara, and C. Jackson, *The impact of comorbidity on cancer and its treatment.* CA Cancer J Clin, 2016. **66**(4): p. 337-50.

12. Gurney, J., D. Sarfati, and J. Stanley, *The impact of patient comorbidity on cancer stage at diagnosis.* Br J Cancer, 2015. **113**(9): p. 1375-80.

13. Sogaard, M., et al., *The impact of comorbidity on cancer survival: a review.* Clin Epidemiol, 2013. **5**(Suppl 1): p. 3-29.

14. Cauley, C.E., et al., *Outcomes after emergency abdominal surgery in patients with advanced cancer: Opportunities to reduce complications and improve palliative care.* J Trauma Acute Care Surg, 2015. **79**(3): p. 399-406.

15. *User, S. (2019). HIGHCARE | Transcan-2 translational cancer research program. [online] Transcanfp7.eu. Available at:* https://www.transcanfp7.eu/index.php/abstract/highcare.html *[Accessed 12 Jan. 2019].*

16. Maringe, C., et al., *Reproducibility, reliability and validity of population-based administrative health data for the assessment of cancer non-related comorbidities.* PLoS One, 2017. **12**(3): p. e0172814.

17. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.

18. Brusselaers, N. and J. Lagergren, *The Charlson Comorbidity Index in Registry-based Research.* Methods Inf Med, 2017. **56**(5): p. 401-406.

19. Agresti, A., *An introduction to categorical data analysis*, in *Wiley series in probability and statistics*. 2018, John Wiley & Sons, Inc.,: Hoboken, New Jersey. p. 1 online resource.

20. Yau, N., *Visualize this : the flowing data guide to design, visualization, and statistics*. 2011, Indianapolis: Wiley. xxvi, 358 p.

21. Sarfati, D., et al., *The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study.* BMC Cancer, 2009. **9**: p. 116.

22. Sarfati, D., et al., *Identifying important comorbidity among cancer populations using administrative data: Prevalence and impact on survival.* Asia-Pacific Journal of Clinical Oncology, 2013.

23. Shaw, J.E., R.A. Sicree, and P.Z. Zimmet, *Global estimates of the prevalence of diabetes for 2010 and 2030.* Diabetes Res Clin Pract, 2010. **87**(1): p. 4-14.

24. Huang, C.W., et al., *The impact on clinical outcome of high prevalence of diabetes mellitus in Taiwanese patients with colorectal cancer.* World J Surg Oncol, 2012. **10**: p. 76.

25. Onitilo, A.A., et al., *Diabetes and cancer I: risk, survival, and implications for screening.* Cancer Causes Control, 2012. **23**(6): p. 967-81.

26. Salas Trejo, D., et al., *Implementation of colorectal cancer screening in Spain: main results 2006-2011.* Eur J Cancer Prev, 2017. **26**(1): p. 17-26.

27. Mandelblatt, J., et al., *The late-stage diagnosis of colorectal cancer: demographic and socioeconomic factors.* Am J Public Health, 1996. **86**(12): p. 1794-7.

28. White, M.C., et al., *Age and cancer risk: a potentially modifiable relationship.* Am J Prev Med, 2014. **46**(3 Suppl 1): p. S7-15.

29. Yancik, R., et al., *Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base.* J Clin Oncol, 2001. **19**(4): p. 1147-51.

30. Renzi, C., et al., *Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England.* Br J Cancer, 2016. **115**(7): p. 866-75.

31. Yancik, R., et al., *Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study.* Cancer, 1998. **82**(11): p. 2123-34.

32. Sun, Z., et al., *Optimal Timing to Surgery after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer.* J Am Coll Surg, 2016. **222**(4): p. 367-74.

33. Shin, D.W., et al., *Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer.* Ann Surg Oncol, 2013. **20**(8): p. 2468-76.

34. Flemming, J.A., et al., *Association between the time to surgery and survival among patients with colon cancer: A population-based study.* Eur J Surg Oncol, 2017. **43**(8): p. 1447-1455.

35. Mayor, S., *One in four cases of bowel cancer in England are diagnosed only after emergency admission.* BMJ, 2012. **345**: p. e7117.

36. Mitchell, E.D., B. Pickwell-Smith, and U. Macleod, *Risk factors for emergency presentation with lung and colorectal cancers: a systematic review.* BMJ Open, 2015. **5**(4): p. e006965.

37. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

38. Piccirillo, J.F., et al., *Prognostic importance of comorbidity in a hospital-based cancer registry.* Jama, 2004. **291**(20): p. 2441-7.

39. Elixhauser, A., et al., *Comorbidity Measures for Use with Administrative Data.* Medical Care, 1998. **36**(1).

40. Sarfati, D., *Review of methods used to measure comorbidity in cancer populations: no gold standard exists.* J Clin Epidemiol, 2012. **65**(9): p. 924-33.

Supporting information

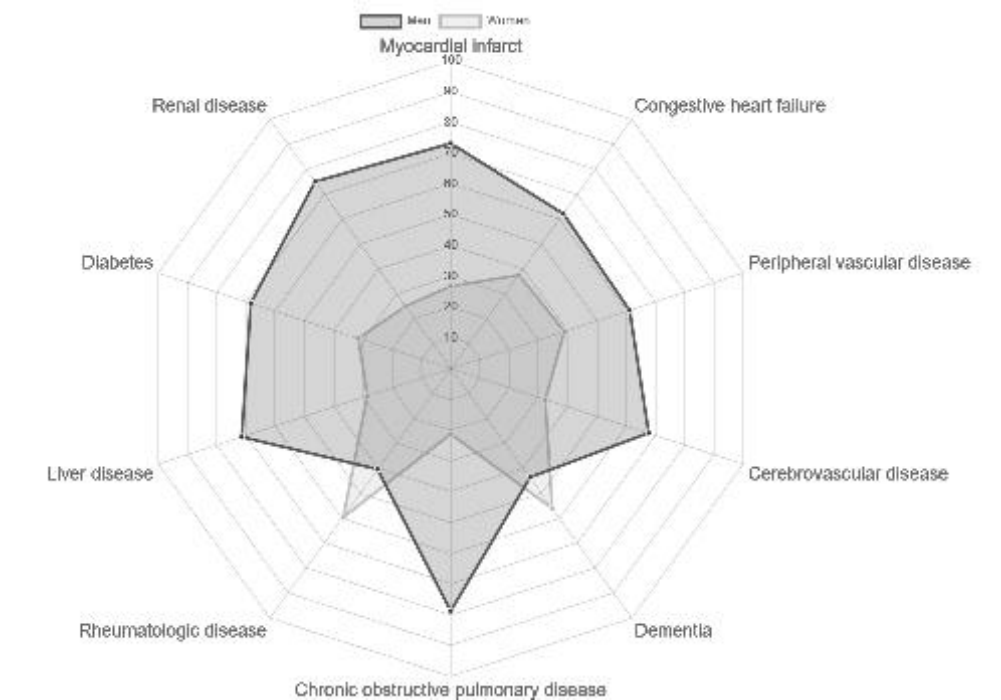
Supplementary Table S1. Ordered prevalence of comorbidities among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

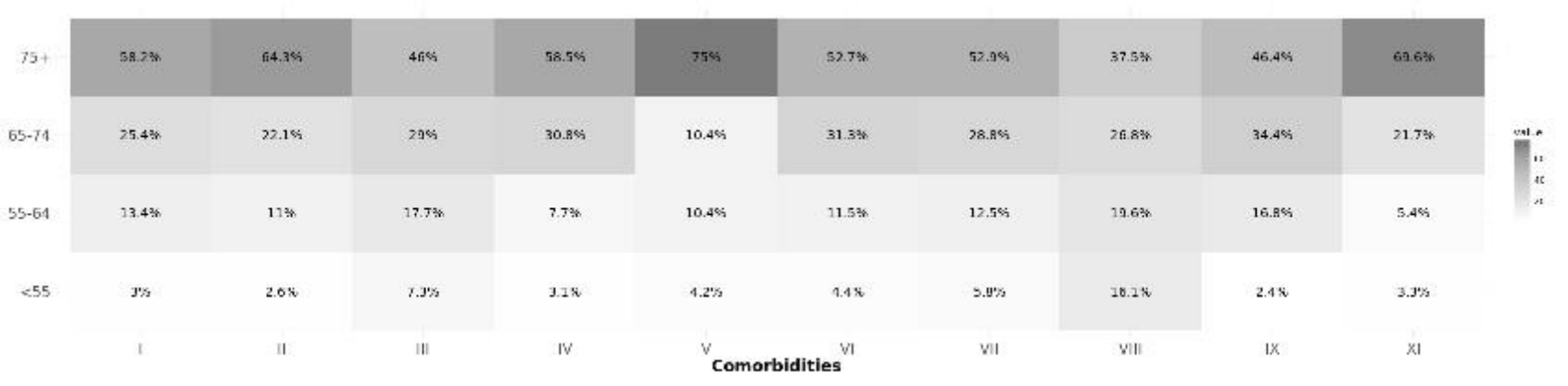
Supplementary Table S2. Risk factors associated with the top-five comorbidities adjusted by sex and age among all incident colorectal cancer patients by patient characteristics during 2011 in Granada and Girona, n = 1,061

Supplementary Table S3. Distribution and frequency of comorbidities by patient's characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Supplementary Table S4. Distribution and frequency of comorbidities by tumor characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061

Supplementary Table S5. Distribution and frequency of comorbidities by healthcare characteristics among all incident colorectal cancer patients in Granada and Girona, 2011, n = 1,061


Men
Women
Myocardial infarct
Congestive heart failure
Peripheral vascular disease
Cerebrovascular disease
Dementia
Chronic obstructive pulmonary disease
Rheumatologic disease
Liver disease
Diabetes
Renal disease
100
90
80
70
60
50
40
30
20
10


75+
65-74
55-64
<55
58.2%
64.3%
46%
58.5%
75%
52.7%
52.9%
37.5%
46.4%
69.6%
25.4%
22.1%
29%
30.8%
10.4%
31.3%
28.8%
26.8%
34.4%
21.7%
13.4%
11%
17.7%
7.7%
10.4%
11.5%
12.5%
19.6%
16.8%
8.4%
3%
2.6%
7.3%
3.1%
4.2%
4.4%
5.8%
10.1%
2.4%
3.3%
I
II
III
IV
V
VI
VII
VIII
IX
XI
Comorbidities

Patient factors / Multimorbidity

Variable	Categories	Risk ratio	Confidence interval
Age			
	55-64 vs <55	2.53	(1.22 - 5.26)
	65-74 vs <55	8.45	(4.25 - 16.81)
	>74 vs <55	14.77	(7.57 - 28.82)
Sex			
	Women vs men	0.65	(0.48 - 0.88)
Performance			
	1 vs 0	4.64	(3.06 - 7.05)
	2 vs 0	6.77	(3.57 - 12.85)
	3-4 vs 0	24.69	(8.13 - 74.99)
BMI			
	25-29.9 vs <25	1.01	(0.66 - 1.54)
	>29.9 vs <25	2.17	(1.36 - 3.46)