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Original Research

Trajectories of health-related quality of life and psychological distress in patients with colorectal cancer: A population-based study

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Abstract ***Background:*** The aim of this nationwide cohort study was to examine the course of symptoms and trajectories of health-related quality of life (HR-QoL) and psychological distress during follow-up and to identify vulnerable patients.
Methods: Patients with pathological stage I–III colorectal cancer (CRC) between 2013 and 2018 were included. Baseline characteristics were collected from the Netherlands Cancer Registry, and patients completed the European Organisation for Research and Treatment of Cancer QLQ-C30/CR29, Hospital Anxiety and Depression Scale and low anterior resection syndrome (LARS) questionnaires at the baseline and subsequently at 3, 6, 12, 18 and 24 months. Latent class growth and multinomial logistic regression analyses were performed to outline 24-month trajectories in HR-QoL and distress and to identify predictive factors.
Results: : A total of 1535 patients with colon cancer or rectal cancer were included. Trajectory analysis of HR-QoL identified three patient classes: high HR-QoL (62.7%), improving HR-QoL (29.0%) and low HR-QoL (8.3%). The following patient groups were identified with having low distress (64.0%), moderate distress (26.9%) and high distress (9.1%). Around 13% of the total cohort had either persistent low HR-QoL or high psychological distress throughout follow-up. Patients belonging to this vulnerable group were significantly more likely to be

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female, to be younger aged, to have lower education, to have disease stage II–III or to have major LARS.

Conclusions: Although most patients treated for stage I–III CRC fared well, a small but significant proportion of around 13% did not recover during follow-up and reported low HR-QoL and/or high psychological distress levels throughout. This study's findings should be taken into account when organising and selecting patients for tailored follow-up.

1. Introduction

Because of earlier diagnosis and improved treatment, the number of colorectal cancer (CRC) survivors increased [1–3]. Relative survival five year after surgery for stage I, II and III is approximately 95%, 90% and 75%, respectively [3]. As per the Dutch colorectal cancer guidelines, patients diagnosed with stage I–III colon are treated surgically. Adjuvant chemotherapy is administered to high-risk stage II and stage III patients [4]. Patients with stage I–II rectal cancer (up to 35%) are treated with local excision or radical surgery only. Patients with stage III rectal cancer undergo neo-adjuvant chemoradiation therapy or short-course radiotherapy followed by surgical resection [4].

After treatment, patients are followed to allow adequate screening and treatment of complications, but also to detect and treat disease recurrence or long-term morbidity [5]. In the Netherlands, CRC follow-up occurs as per the national guidelines and usually consists of biannual clinical visits, laboratory tests and imaging tests [Appendix 1].

The diagnosis and treatment of CRC have a high burden on patients' well-being. This includes physical as well as psychological distress [6–9]. The symptoms such as abdominal pain, fatigue, diarrhoea, flatulence, changed stool and urinary frequency and sexual impairment have been reported during the first post-operative year and thereafter [10]. Psychological distress, on the other hand, also affects patients with CRC [11,12]. Fortunately, most symptoms diminish during follow-up, and it has been shown that health-related quality of life (HR-QoL) normalises after one year [10]. Nonetheless, enduring symptoms long after initial (surgical) treatment impair patients' HR-QoL [13].

Previous studies found that, overall, HR-QoL of CRC survivors was comparable with the normative population, but that deficits in functional scores and various physical symptoms were reported [14,15]. In a systematic review, good overall HR-QoL but worse depression scores, distress and bowel problems were demonstrated [16]. Psychological distress was prevalent in up to 44% of all participants, and trajectories with high distress were, among others, differentiated by gender, age, education and disease stage [11]. Many of these results were based on data from more than a decade ago [14,17]. Over the years, earlier diagnosis, improved (neo)-adjuvant therapies, minimal invasive surgery and more accurate detection of disease recurrence have improved recovery and survival [1]. Moreover, personalised care improved because of availability of case managers and specialised nurses and better information provision [18,19].

Because adequate identification of patients with persisting symptoms or psychological distress is needed to provide patient-centred, tailored follow-up care, the aim of this study was to determine the course of symptoms and trajectories of psychological distress and HR-QoL during follow-up of patients with CRC and to identify patient groups that might require additional care.

2. Material and methods

2.1. Study design and data collection

Data from the ongoing, prospective population-based Prospective Dutch Cohort CRC (PLCRC) study were analysed. The PLCRC study population was found to be representative for the general Dutch CRC population [20]. Details of the data collection were published previously [21]. The Netherlands Cancer Registry (NCR) registers all newly diagnosed patients with cancer in the Netherlands [22]. Briefly, all patients diagnosed with CRC are eligible for participation in the PLCRC study. Patients received information about the study, and written consent was obtained. Participants were asked to complete questionnaires at study enrolment and subsequently at 3, 6, 12, 18 and 24 months. Ethical approval for the PLCRC study was obtained from the Medical Ethics Committee of Utrecht (number 12-510). PLCRC is registered at Clinicaltrials.gov (NCT02070146).

2.2. Patient selection and measures

Patients diagnosed with pathological stage I–III CRC who underwent curative surgical or endoscopic treatment between 2013 and 2018 were selected. For this study, patients who were <6 months in follow-up at

enrolment (baseline) and had at least filled in one subsequent questionnaire were included (N = 1535).

2.2.1. Sociodemographic and clinical characteristics

Patients' sociodemographic and clinical information was retrieved from the NCR. Comorbidity was assessed with the adapted Self-administered Comorbidity Questionnaire [23]. Questions on marital status, educational level, body mass index and stoma information were added. A higher educational level was defined as having at least a college or a university degree. Tumour localisation was categorised using the International Classification of Disease for Oncology into colon (C18.0–18.9) and rectum (C19.9–20.9) [24]. Disease stage was based on the pathological tumour lymph node metastasis (TNM-7 and -8 editions) classification.

2.2.2. Patient-reported outcomes

HR-QoL was assessed by the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 (general HR-QoL) and QLQ-CR29 (colorectal-specific QoL) [25]. EORTC-C30 values from a general population sample were used for comparison [26]. The QLQ-CR29 submodule specifically assesses CRC symptoms [27]. Raw scores for each scale were linear transformed into a 0–100 outcome. A higher functioning score indicated better functioning or global health/QoL, whereas higher symptom scores indicated a higher level of symptom severity. A minimum important clinically difference of 5–10 points (small), 10–20 (moderate) and ≥20 (large) was used for interpreting group differences and changes in the EORTC-QLQ-C30 and QLQ-CR29 scores [28]. In addition, the EORTC QLQ-C30 summary score was calculated as the mean of the combined 13 C30 scale and item scores (excluding global health/QoL and financial impact), with a higher score indicating better HR-QoL [29]. Cronbach's α was 0.93 for the QLQ-C30 and 0.77 for the QLQ-CR29 in this study.

Total scores of the low anterior resection syndrome (LARS) questionnaire were used to assess to what extent patients experienced bowel dysfunction [30]. It classifies patients into no LARS (0–20 points), minor LARS (21–29 points) or major LARS (30–42). Cronbach's α was 0.74 in this study.

The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress. It includes 14 items divided into two subscales, depression and anxiety, both containing 7 items. A total score of 11 or higher indicated psychological distress [31,32]. Reference HADS scores from a general population sample were used for comparison [33]. Cronbach's α was 0.89 in this study.

2.3. Statistical analysis

2.3.1. Descriptive statistics

Continuous variables are depicted as means and standard deviations, and categorical variables, as frequencies and percentages. Differences in characteristics were examined using chi-square, t-test or analysis of variance.

2.3.2. Trajectory analyses

Latent class growth analysis (LCGA) in MPlus was conducted to identify trajectories (classes) for the EORTC-C30 summary score and HADS total scores, according to Jung and Wickrama [34]. LCGA estimates individual differences (variability) in parameters, reflecting participants' change in outcomes over time. Individuals are classified into latent classes based on similar patterns in the outcome of interest (i.e. HR-QoL, distress). LCGA assumes no within-class variation on the growth factors. Thus, all individual longitudinal trajectories within a subgroup are considered to be homogeneous, leading to a clearer identification of classes. MPlus' full information maximum likelihood estimation for handling missing data was applied. The number of trajectories was determined based on fit indices, model parsimony and clinical interpretability. Methodological details on the determination of the best fit number of trajectories are available in Appendix 2A.

Hereafter, predictors for class membership were identified using multinomial logistic regression analysis. First, sociodemographic, treatment-related and patient-reported variables were tested individually for significance. The significant variables were then included in two separate models for HR-QoL and distress. The ratio of the probability for class membership (in comparison with the reference) is referred as the relative risk ratio (RRR). Regression results were displayed in terms of RRRs.

Analyses were performed using Stata software (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and MPLUS (Version 6.11, Los Angeles, CA: Muthén & Muthén). Two-sided analyses with $P < 0.05$ were considered as significant. We adhered to the STROBE checklist for observational cohort studies [35].

3. Results

3.1. Sociodemographic information

A total of 825 patients with colon cancer (CC) and 710 patients with rectal cancer (RC) were included. The median age at diagnosis was, respectively, 66 (interquartile range [IQR] 14) and 65 (IQR 13) for CC and

RC. Most patients were living together (CC 78% and RC 63%), and 68% of the patients with CC and 78% of the patients with RC had at least finished secondary education. Baseline questionnaires were filled in at a median follow-up of 1.3 (IQR 1.3) months from diagnosis. The corresponding median follow-up from treatment was 1.0 (IQR 1.0) month at the baseline. Response rates for the different questionnaires ranged from 84% to 100% at the baseline, 66–85% at 3-month follow-up, 60–82% at 6-month, 59–76% at 12-month, 47–61% at 18-month and 31–42% at 24-month follow-up. The median (vital status) follow-up from diagnosis for the total group was 14 months (IQR 19). Baseline characteristics and patient reported outcome measures at the baseline are presented in Tables 1 and 2.

3.2. Symptom burden, psychological distress and HR-QoL at the baseline and follow-up

Compared with the baseline, global health/HR-QoL and all functioning scales except cognitive and physical functioning improved slightly moderately within 24-month follow-up. The latter two remained stable. In the first 6 months, patients with RC reported a slightly deteriorated (5–10 points) role, social, cognitive and physical functioning. Concerning the same scales, patients with CC showed a faster recovery than patients with RC (within 12 months). For patients with CC, global health/HR-QoL, role and social functioning normalised to healthy individuals' reference levels within 12 months, whereas patients with RC needed more time [Fig. 1]. From the baseline, emotional scores of patients with CRC were better than those in the healthy population. Cognitive and physical scores, on the other hand, were similar to the reference population. The mean EORTC summary score for patients with CC and RC at the baseline was 82.2 (standard deviation [SD] 14.9) and 84.5 (SD 13.6), respectively [Table 2]. These scores increased slightly (>5 points) during the course of follow-up.

Regarding symptom severity scores, a slight-moderate decline in gastrointestinal and stoma-related symptoms was reported by patients with RC at 3–6 months (compared with the baseline). After 12-month follow-up, most symptom scores improved compared with the baseline, except for defecation problems for RC and weight loss for both RC and CC.

After an initial worsening of LARS severity 3 months after baseline in patients with RC, no further changes were noted. At 24 months, 44% reported major LARS [Fig. 2A]. Mean LARS scores of patients with CC did not improve or deteriorate over time. In comparison with the baseline, the proportion of no LARS increased in patients with CC and decreased in patients with RC over time [Fig. 2B].

Mean baseline scores of HADS total and subscale scores of anxiety and depression of patients with CC were 7.4 (SD 6.3), 4.1 (3.6) and 3.4 (3.4), respectively. Patients with RC had similar scores [Table 2]. Baseline HADS total and subscale values reported here were significantly lower than those in the healthy reference population ($P < 0.001$) [33]. Compared with the baseline, both HADS total and subscale scores of anxiety and depression, as well as the proportion of patients with high distress, were lower at subsequent follow-up moments [Fig. 3]. At the baseline, no difference in global health/HR-QoL was found between patients with CC and RC (71.9 vs. 73.9). Role functioning was slightly better (6 points) in patients with RC, but these patients reported more defecation and gastrointestinal symptoms within the range of small to moderate clinical significance.

Table 1
Characteristics of patients with stage I–III colon or rectal cancer at study enrolment (baseline) (N = 1535).

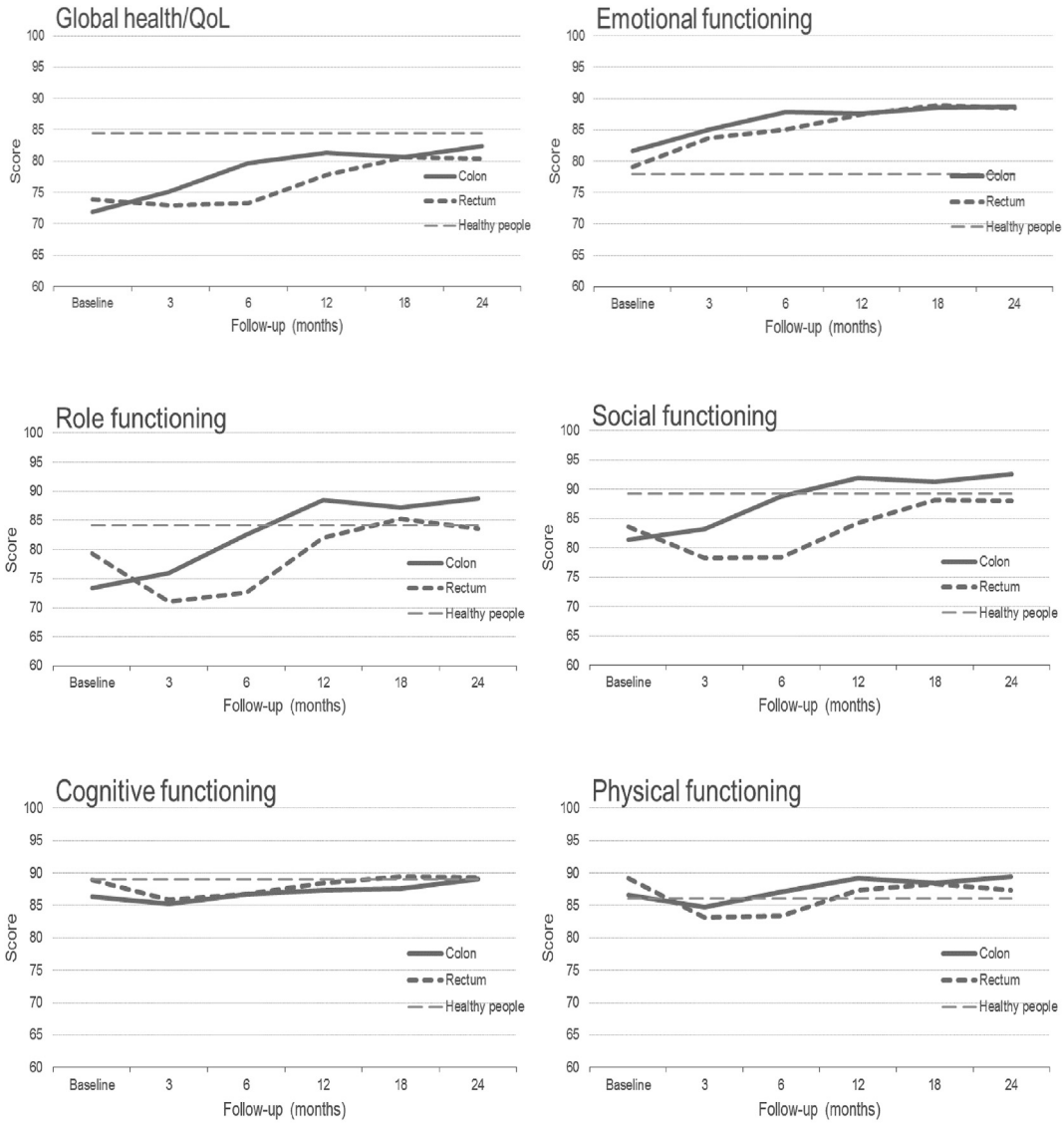
N (%) or median (IQR)	Colon cancer (N = 825)	Rectal cancer (N = 710)	P value
Gender			<0.01[a]
Male	510 (62)	492 (69)	
Female	315 (38)	218 (31)	
Age at diagnosis	66 (14)	65 (13)	<0.07
Year of diagnosis			N/A
2013–2014	3 (<1)	117 (17)	
2015–2016	157 (19)	144 (20)	
2017–2018	665 (81)	449 (63)	
Time from diagnosis (months)	1.4 (1.6)	1.2 (0.9)	0.10
Pathological stage			<0.01[a]
I	229 (28)	158 (22)	
II	252 (30)	128 (18)	
III	344 (42)	424 (60)	
Surgical resection			<0.01[a]
Yes	814 (99)	664 (94)	
No	11 (1)	46 (6)	
Type of resection			<0.01[a]
Colectomy[b]	466 (56)	1 (<1)	
Sigmoid resection	249 (30)		
LAR	46 (6)	442 (62)	
APR	1 (<1)	198 (28)	
Subtotal or proctocolectomy	26 (3)	2 (<1)	
Local excisions[c]	37 (4)	65 (9)	
Missing		2 (<1)	
Chemotherapy			<0.01[a]
No	504 (61)	374 (52)	
Neo-adjuvant	8 (1)	282 (40)	
Adjuvant	312 (38)	45 (6)	
Pre- and post-operative	1 (<1)	5 (1)	
Yes, no surgery	0 (0)	4 (1)	
Radiation therapy			<0.01[a]
No	819 (99)	231 (33)	
Neo-adjuvant	5 (1)	461 (65)	
Adjuvant	0 (0)	6 (1)	
Pre- and post-operative	1 (<1)	8 (1)	
Yes, no surgery	0 (0)	4 (1)	
Stoma			<0.01[a]
No	763 (92)	366 (52)	
Yes	62 (8)	344 (48)	

IQR, interquartile range; LAR, low anterior resection.
[a] Statistically significant using the t-test or chi-square test.
[b] Hemicolectomy/right or left (extended) colectomy.
[c] Local or endoscopic excision.

Table 2
Course of patient-related outcome measures over time in patients treated for stage I–III colon or rectal cancer.

N (%) or mean (SD)	Study enrolment		3 months		6 months		12 months		24 months	
	Colon N = 825	Rectum N = 710	Colon N = 712	Rectum N = 590	Colon N = 684	Rectum N = 583	Colon N = 624	Rectum N = 549	Colon N = 303	Rectum N = 339
Age	65.5 (9.6)	64.4 (9.7)	65.8 (9.7)	64.5 (9.4)	65.5 (9.6)	64.7 (9.6)	65.6 (9.5)	65.0 (9.3)	66.0 (8.6)	64.9 (9.2)
Functional scales EORTC QLQ-C30										
Global health/QoL	71.9 (20.0)	73.9 (19.4)	75.2 (19.2)	72.9 (18.7)	79.7 (15.9)	73.3 (18.4)	81.3 (16.4)	77.8 (16.9)	82.4 (15.4)	80.4 (16.2)
Emotional functioning	81.6 (18.9)	79.1 (19.4)	85.0 (17.5)	83.7 (18.7)	87.8 (16.2)	85.0 (18.2)	87.6 (16.6)	87.5 (16.4)	88.7 (15.6)	89.4 (14.6)
Social functioning	81.4 (23.2)	83.6 (21.5)	83.2 (21.0)	78.3 (24.1)	88.8 (17.9)	78.4 (23.4)	91.9 (15.5)	84.2 (21.0)	92.5 (15.4)	88.0 (18.6)
Cognitive functioning	86.3 (18.3)	88.9 (16.3)	85.3 (18.7)	85.9 (18.0)	86.2 (18.5)	86.7 (17.2)	87.3 (16.5)	88.4 (16.8)	89.1 (15.5)	89.3 (15.1)
Role functioning	73.3 (31.9)	79.3 (28.6)	75.9 (26.5)	71.1 (29.2)	82.6 (23.3)	72.6 (29.7)	88.5 (19.8)	82.0 (23.6)	88.7 (19.6)	83.6 (23.3)
Physical functioning	86.6 (17.0)	89.2 (16.0)	84.8 (16.6)	83.1 (18.3)	87.1 (15.6)	83.4 (18.2)	89.2 (15.1)	87.3 (14.9)	89.5 (14.3)	87.4 (16.0)
Summary score EORTC QLQ-C30	82.2 (14.9)	84.5 (13.6)	84.2 (13.9)	82.8 (14.2)	87.5 (12.2)	83.8 (14.5)	89.4 (11.4)	87.6 (11.6)	90.3 (10.4)	89.0 (11.3)
Symptom scales EORTC QLQ-C30										
Fatigue	29.1 (25.3)	24.1 (24.3)	27.4 (24.5)	29.0 (24.4)	22.7 (22.3)	27.2 (24.5)	18.7 (19.8)	20.6 (19.9)	17.5 (19.7)	18.8 (19.8)
Nausea and vomiting	7.3 (16.7)	5.1 (13.0)	6.5 (14.8)	3.7 (10.8)	3.3 (10.4)	3.6 (11.4)	2.5 (8.9)	2.7 (9.4)	2.0 (6.6)	2.4 (8.8)
Pain	17.2 (23.5)	15.3 (23.7)	13.1 (20.1)	17.8 (24.6)	10.2 (18.8)	17.3 (25.0)	9.1 (17.5)	11.5 (20.3)	7.9 (16.6)	9.6 (18.1)
Dyspnoea	12.6 (21.3)	7.2 (16.3)	13.4 (22.9)	9.7 (18.4)	11.9 (20.5)	9.0 (17.7)	10.7 (19.9)	9.5 (17.5)	9.1 (18.2)	8.8 (16.8)
Insomnia	24.0 (29.0)	23.9 (29.3)	18.7 (24.9)	23.8 (28.8)	18.3 (25.1)	22.5 (27.4)	16.8 (23.9)	18.8 (25.5)	16.3 (22.7)	16.6 (23.3)
Appetite loss	14.2 (25.7)	10.5 (21.1)	12.3 (24.0)	10.2 (21.7)	5.3 (15.4)	10.2 (22.0)	4.7 (15.6)	4.3 (14.3)	3.5 (11.9)	4.0 (14.3)
Constipation	10.1 (20.1)	11.9 (22.0)	8.7 (17.7)	9.8 (21.1)	6.8 (15.4)	7.7 (17.8)	6.9 (16.1)	7.7 (17.1)	6.7 (15.5)	5.9 (14.9)
Diarrhoea	17.6 (25.4)	19.8 (25.6)	12.9 (22.9)	13.7 (24.7)	11.2 (20.4)	10.1 (21.3)	9.0 (19.4)	10.8 (20.2)	8.6 (18.4)	8.9 (18.9)
Financial difficulties	4.7 (14.5)	4.5 (14.1)	4.7 (13.7)	6.1 (17.2)	4.5 (14.1)	6.3 (17.0)	4.6 (14.3)	6.7 (17.6)	4.9 (14.6)	5.0 (14.7)
Symptom scales EORTC-CR29										
Micturition	18.0 (13.2)	18.8 (14.9)	16.0 (13.0)	19.6 (14.2)	15.3 (12.9)	18.8 (15.1)	14.4 (12.9)	17.0 (14.0)	14.8 (12.7)	17.2 (14.5)
Defecation	15.8 (14.9)	24.7 (18.1)	14.8 (14.0)	26.8 (19.7)	13.4 (13.3)	28.2 (19.9)	12.6 (11.8)	26.5 (17.5)	11.8 (12.0)	25.0 (16.6)
Gastrointestinal	12.6 (13.8)	20.2 (16.1)	7.8 (10.3)	13.9 (13.9)	6.1 (9.7)	11.9 (13.4)	6.3 (9.8)	9.3 (11.0)	4.5 (7.5)	7.4 (10.1)
Chemotherapy side-effects	10.7 (14.9)	7.8 (11.9)	14.1 (16.5)	10.3 (13.6)	10.3 (13.9)	9.4 (13.2)	6.6 (10.6)	8.2 (12.3)	7.0 (11.1)	8.2 (13.1)
Stoma-related	17.2 (13.2)	20.6 (15.5)	16.0 (10.3)	19.4 (15.6)	17.2 (10.2)	17.7 (13.3)	16.4 (15.3)	14.2 (11.5)	19.2 (11.8)	11.1 (8.8)
Weight loss	12.2 (20.8)	11.3 (20.2)	12.3 (20.5)	13.3 (20.9)	13.4 (21.9)	14.4 (21.6)	13.4 (21.3)	13.7 (20.6)	11.4 (20.0)	14.0 (20.2)
LARS score	15.7 (12.2)	22.8 (12.9)	15.9 (12.1)	25.3 (12.4)	15.1 (11.7)	24.9 (12.1)	14.3 (11.4)	25.1 (12.0)	14.1 (11.4)	24.8 (11.9)
LARS classification[a]										
No	515 (66)	207 (41)	434 (65)	116 (33)	446 (69)	95 (36)	424 (71)	109 (35)	200 (71)	76 (38)
Minor	151 (19)	113 (22)	121 (18)	70 (20)	107 (16)	59 (22)	96 (16)	64 (20)	49 (17)	35 (18)
Major	120 (15)	191 (37)	111 (17)	167 (47)	96 (15)	111 (42)	74 (13)	142 (45)	33 (12)	89 (44)
Anxiety and depression HADS										
Total	7.4 (6.3)	7.6 (6.5)	6.4 (5.8)	6.8 (6.1)	6.0 (5.7)	6.9 (5.9)	6.0 (5.7)	6.1 (5.6)	5.6 (5.3)	5.6 (5.2)
Anxiety	4.1 (3.6)	4.3 (3.7)	3.2 (3.1)	3.4 (3.2)	3.1 (3.1)	3.3 (3.1)	3.1 (3.1)	3.1 (3.1)	2.9 (2.9)	2.7 (2.9)
Depression	3.4 (3.4)	3.3 (3.5)	3.1 (3.4)	3.4 (3.5)	2.9 (3.2)	3.5 (3.3)	2.9 (3.2)	3.0 (3.1)	2.7 (2.9)	2.9 (3.0)

SD, standard deviation; QoL, quality of life; EORTC, European Organisation for Research and Treatment of Cancer; LARS, low anterior resection syndrome; HADS, Hospital Anxiety and Depression Scale.
Baseline <6 months of follow-up.
[a] 0–20: no LARS, 21–29: mild LARS, 30–42: severe LARS. Numbers do not always add up to 100% because of rounding to whole numbers.



N	Baseline	3-months	6-months	12-months	18-months	24-months
Colon	825	712	684	624	486	303
Rectum	710	590	583	549	457	339

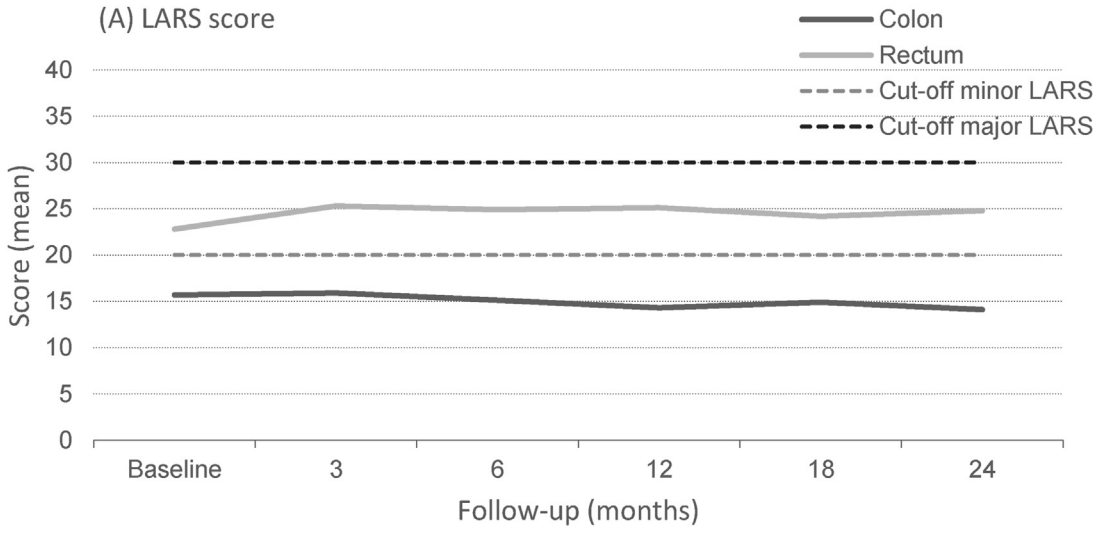
Fig. 1. Mean HR-QoL function scale scores (EORTC-QLQ-C30) over time (scale 0–100). A higher functioning score indicates better functioning or global health/HR-QoL. EORTC, European Organisation for Research and Treatment of Cancer; HR-QoL, health-related quality of life.

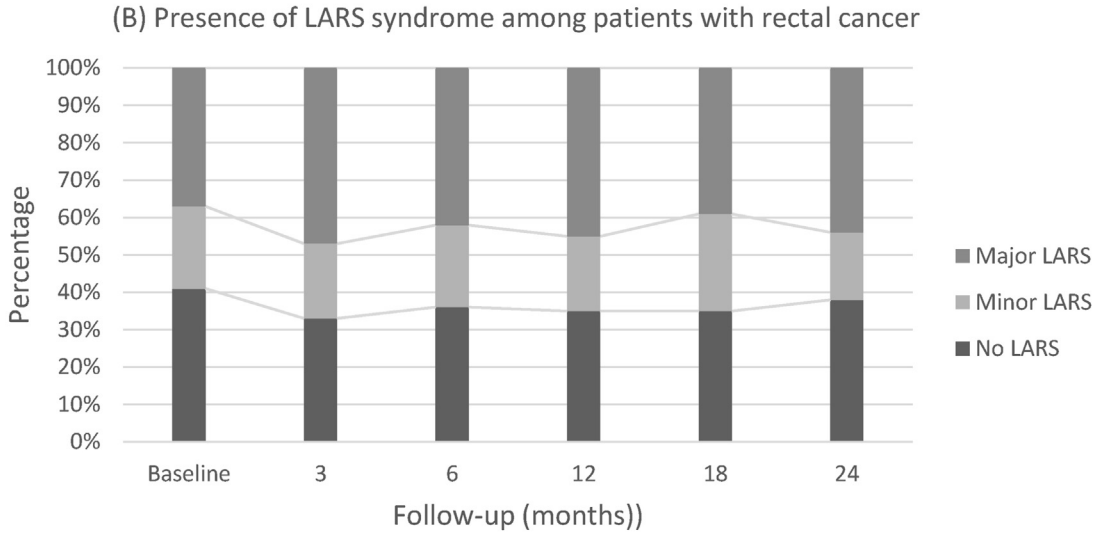
Patients with CC reported slightly more fatigue and dyspnoea (≥5 points). Mean LARS scores were, respectively, 15.7 (SD 12.2) and 22.8 (SD 12.2) for patients with CC and RC ($P < 0.01$), with, respectively, 15% and 37% major LARS for patients with CC and RC.

3.3. Trajectories of HR-QoL and predictors for low, improving and high HR-QoL

Using trajectory analysis, clusters of patients with similar HR-QoL were assessed over a 24-month period.

For HR-QoL, a three-class model was identified as the best fit [Table 3, Appendix 2B]. The first subgroup (n = 962, 62.7%) was defined as 'high HR-QoL', with an intercept of 89.44 (95% confidence interval [CI] 88.4–90.5) and a slope of 1.37 (95% CI 1.2–1.5, significant). The second subgroup was defined as 'improving HR-QoL', as the 446 (29.0%) participants in this group showed moderate to high baseline QoL scores (intercept 76.32; 95% CI 74.9–77.8), and the slope was 1.6 (95% CI 1.1–2.1, significant). The third subgroup (n = 127, 8.3%) was defined as 'low HR-QoL', as





N	Baseline	3-months	6-months	12-months	18-months	24-months
Colon	825	712	684	624	486	303
Rectum	710	590	583	549	457	339

Fig. 2. LARS scores among patients with colon and rectal cancer (A) and the presence of LARS among patients with rectal cancer (B). A higher score indicates more LARS. LARS, low anterior resection syndrome.

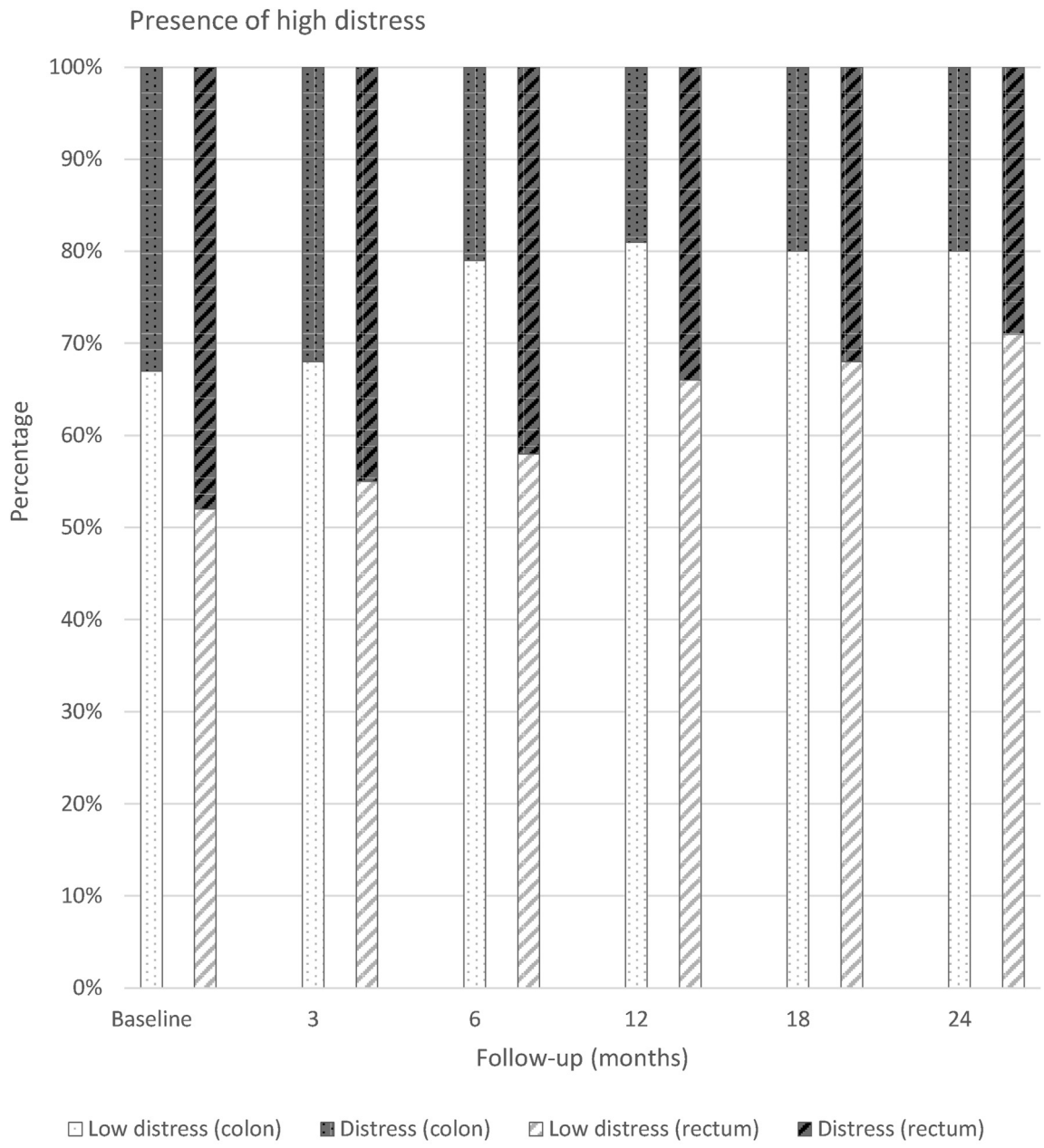
participants reported low baseline HR-QoL scores (intercept 63.5; 95% CI 59.2–67.9), and the slope was 0.03 (95% CI −0.9 to 0.9, non-significant).

Compared with patients in the 'high HR-QoL class' (reference), patients in the improving and low HR-QoL classes were significantly more likely to be female, to have lower education or to have major LARS. Those in the improving class were also more likely to have disease stage II–III or underwent radiotherapy. Undergoing an abdomino-perineal resection (improving class), sigmoid resection or an LAR decreased the chance of belonging in the low class [Table 4].

3.4. Trajectories of psychological distress and predictors for low, moderate and high distress

Likewise, classes of patients with similar psychological distress were assessed over 24-month follow-up, resulting in a three-class model [Table 3, Appendix 2B].

The first subgroup (n = 920, 64.0%) was defined as 'low distress', with an intercept of 4.0 (95% CI 3.7–4.4) and a slope of −0.3 (95% CI −0.3 to −0.2, significant). The second subgroup was defined as 'moderate distress', as the 387 (26.9%) participants showed moderate baseline HADS total scores (intercept 10.0; 95% CI 9.1–10.9), and the



N	Baseline	3-months	6-months	12-months	18-months	24-months
Colon	825	712	684	624	486	303
Rectum	710	590	583	549	457	339

Fig. 3. Presence of psychological distress (HADS total score ≥11) over time. Colon cancer: dotted, rectal cancer: striped. HADS, Hospital Anxiety and Depression Scale.

slope was −0.1 (95% CI -0.3−0.1, non-significant). The third subgroup (n = 130, 9.1%) was defined as 'high distress', as participants reported high baseline HADS scores (intercept 18.6; 95% CI 17.0−20.2), and the slope was −0.1 (95% CI -0.5−0.2, non-significant).

Compared with patients in the low distress class (reference), patients in the moderate and high distress classes were more likely to be younger, to have lower education or to have major LARS [Table 4].

Of the total cohort of 1535 patients, 200 (13%) belonged either to the low HR-QoL class or to the high distress class. A total of 57 of 127 (45%) patients belonging to the low HR-QoL class also belonged to the high distress class.

Table 3
Fit indices and class characteristics of HR-QoL and distress trajectories.

Variable	No. of classes	BIC	LMR-LRT	BLRT	Entropy	N (%)	Posterior probabilities	Intercept (95% CI)	Slope linear (95% CI)
HR-QoL	3	51579.1	0.0147	0.0000	0.796	962 (62.7%)	0.930	89.44 (88.40; 90.48)*	1.37 (1.20; 1.54)*
						446 (29.0%)	0.838	76.32 (74.87; 77.76)*	1.60 (1.09; 2.12)*
						127 (8.3%)	0.919	63.52 (59.15; 67.9)*	0.03 (−0.88; 0.94)
Psychological distress	3	34007.5	0.0011	0.0000	0.848	920 (64.0%)	0.943	4.00 (3.65; 4.35)*	−0.27 (−0.34; −0.2)*
						387 (26.9%)	0.887	9.98 (9.05; 10.91)*	−0.11 (−0.28; 0.07)
						130 (9.1%)	0.941	18.55 (16.95; 20.15)*	−0.12 (−0.47; 0.23)

HR-QoL, health-related quality of life; BIC, Bayesian information criterion; LMR-LRT, Vuong-Lo-Mendell Rubin likelihood ratio test; BLRT, bootstrap likelihood ratio test; CI, confidence interval.
*P < 0.001.

4. Discussion

This large population-based study investigated symptom burden, psychological distress and HR-QoL among patients treated for stage I–III CRC. Recently diagnosed patients who were less than 6 months in follow-up were surveyed at enrolment and subsequently up to 24 months. Overall, the vast majority of patients with CRC did well and reported high scores on functional QoL scales at the baseline (<6 months of follow-up). For this group, scores continued to improve over time and were comparable with those of the general (reference) population by 12-month follow-up. Trajectory analyses, however, revealed vulnerable patient groups who reported severe HR-QoL deteriorations and high psychological distress during follow-up. Various risk

Table 4
Factors associated with class membership of HR-QoL and distress 24-month trajectories.

	Relative risk ratio (95% confidence interval)					
	HR-QoL			Psychological distress		
	Class 1 962 (62.7%) High HR-QoL	Class 2 446 (29.1%) Improving HR-QoL	Class 3 127 (8.3%) Low HR-QoL	Class 1 920 (64.0%) Low distress	Class 2 387 (26.9%) Moderate distress	Class 3 130 (9.1%) High distress
Sex						
Female	Ref.	1.67 (1.27; 2.19)**	1.60 (1.02; 2.50)*	Ref.	1.14 (0.87; 1.50)	1.31 (0.87; 1.96)
Age		0.99 (0.98; 1.01)	0.99 (0.97; 1.01)		0.98 (0.96; 0.99)**	0.97 (0.95; 0.99)*
Educational level						
Secondary		0.73 (0.52; 1.03)	0.75 (0.44; 1.28)		1.05 (0.75; 1.46)	0.70 (0.43; 1.16)
Higher/university		0.59 (0.42; 0.82)**	0.24 (0.13; 0.46)**		0.61 (0.43; 0.85)**	0.38 (0.22; 0.64)**
Living situation						
Together		0.79 (0.55; 1.15)	0.70 (0.38; 1.28)		N/A	N/A
Disease stage						
II		1.87 (1.26; 2.77)**	1.18 (0.59; 2.38)		0.90 (0.62; 1.32)	1.36 (0.77; 2.39)
III		1.78 (1.14; 2.80)*	1.30 (0.59; 2.86)		1.45 (0.94; 2.22)	1.01 (0.51; 2.03)
Surgical treatment						
Sigmoid resection		1.03 (0.71; 1.50)	0.46 (0.23; 0.94)*		N/A	N/A
LAR		0.75 (0.49; 1.16)	0.40 (0.19; 0.87)*			
APR		0.38 (0.20; 0.74)**	0.17 (0.05; 0.53)**			
Local excision		1.33 (0.76; 2.34)	0.57 (0.20; 1.67)			
Stoma						
Yes		N/A	N/A		1.10 (0.73; 1.64)	1.15 (0.62; 2.15)
Chemotherapy						
Yes		1.13 (0.78; 1.64)	1.85 (0.97; 3.51)		0.84 (0.58; 1.22)	1.46 (0.81; 2.61)
Radiotherapy						
Yes		1.70 (1.10; 2.63)*	1.99 (0.91; 4.34)		1.18 (0.79; 1.76)	0.80 (0.42; 1.53)
LARS						
Major		2.26 (1.66; 3.08)**	3.78 (2.32; 6.15)**		1.85 (1.37; 2.50)**	2.07 (1.33; 3.22)**

LARS, low anterior resection syndrome; Ref: reference; HR-QoL: health-related quality of life; N/A: not applicable: These factors were not significant in the independent, univariate models and therefore not included in the final models.
Statistically significant with P < 0.01** or P < 0.05*.
Fit characteristics of the HR-QoL model: N = 1,295, likelihood ratio chi-square of 168.31 with a P-value of <0.00001 (baseline relative risk of each outcome was 0.22 [0.03; 1.54]).
Fit characteristics of the distress model: N = 1,285, likelihood ratio chi-square of 8.77 with a P-value of <0.00001 (baseline relative risk of each outcome was 1.59 [0.57; 4.45]).

factors for a suboptimal course of HR-QoL and distress were identified.

In the first months of follow-up, consequences of CRC treatment resulted in lower role, social and physical functioning scores, predominantly in patients with RC, who also needed more time to recover than patients with CC. At 12-month follow-up, global health/HR-QoL, as well as other functioning scales, normalised for most patients [14], which is in line with previous studies [10,17,36,37]. For instance, from the baseline, emotional scores of patients with CRC were better than those in the healthy population. In line with the ameliorated emotional functioning of patients with CRC, also anxiety and depression symptom scores (expressed as HADS total and subscale scores) were better in the CRC population than those in the reference population. One explanation for these findings may be more and intensified psychosocial care by healthcare professionals and/or social support by family and friends after cancer diagnosis leading to increased emotional well-being. These findings could also indicate that CRC survivors adapt well to their new situation and successfully cope with possible consequences [38,39], or it might point to a change in their perception on what health or quality of life means to them, also known as response shift.

In comparison with a large-scale study by Arndt et al. [40], especially emotional, social, physical and global health/HR-QoL scores are substantially higher in the present study. Ongoing improvements in technical and surgical innovations such as minimal-invasive surgery could also have contributed to the high levels of HR-QoL [41]. Performing trajectory analyses made it possible to cluster patients with similar HR-QoL or psychological distress patterns over time. The vast majority of patients fared well and belonged to the high HR-QoL and low distress classes. They reported excellent HR-QoL and low psychological distress levels. Another group of around 29–40% reported improving HR-QoL and distress initially, but improved rapidly over time. These patients appear to be resilient, but possess risk factors that make them vulnerable which emphasises the importance of early screening and provision of (supportive) care. A small group of approximately 13% was identified who reported either low, not improving HR-QoL or stable high levels of psychological distress throughout 24-month follow-up. These patients should be monitored carefully and counselled for additional care, with potentially more frequent contact (face-to-face/remote), support by the case-manager or nurse or referral to supportive care specialists (i.e. psychologists and physical therapists) [19]. For instance, early results demonstrated that cognitive behavioural therapy reduced levels of distress in patients with CRC [42], and for a selection of (rectal cancer) patients, pelvic floor rehabilitation might provide relief in LARS-like symptoms [43].

The presence of major LARS, younger age and female gender were risk factors for belonging to the poor performing group. Younger age [14] and female gender [44] have been reported earlier as prognosticators for psychological distress. The presence of distress has shown to compromise health outcomes and quality of life. Anxiety and depressive symptoms are prevalent among surgical patients, and patients with colorectal cancer, in particular, are at risk because of emotional stress due to risk of complication, ostomy and gastrointestinal function [8,12]. Disease stage II–III (only significant in HR-QoL) and receipt of radiotherapy were also associated with an improving HR-QoL compared with those with a high HR-QoL. Having undergone an APR, sigmoid resection or an LAR decreased the chance of belonging in the low class. A higher level of education and older age (only in psychological distress) were found as protective features in maintaining high QoL and low psychological distress. Psychological distress levels in this study were lower than those reported in previous studies, in which rates up to 42% were reported [6,11]. Improved communication of health information, shared decision-making, better treatment regimens and supportive care could have improved self-efficacy and thereby relieved psychological distress for a substantial part of patients [18,19]. Within 24-month follow-up, the proportion of major LARS in patients with RC ranged from 39% to 47%. Other studies found similar rates up to 55% in RC [45] and 21% in CC [46]. On the other hand, also approximately 15% of patients with CC experienced major LARS, whereas only a minority of these patients are operated in the pelvis. This might be explained because similar major LARS is reported in the general population [47]. The percentages of the patients with major LARS did not diminish over time, which is why an improved focus on early screening of LARS-like complaints is necessary to identify patients in need and provide the necessary supportive care. Early results of the FORCE trial showed promising results of protocolised pelvic floor rehabilitation in selective patients with rectal cancer suffering of LARS [43]. Besides that, medication (laxatives/loperamide) or rectal irrigation could provide relief of symptoms.

The findings of this large population-based study present valuable and important information for patients, physicians and policy-makers. Nonetheless, the study has some limitations. First, the sampling design might have missed ill patients who did not want to participate, leading to a risk of overestimating patient-reported outcomes. However, a recent study demonstrated that patients registered in the PLCRC study were comparable with patients in the nationwide cancer registry for all studied factors {Derksen, 2021 #671}. Second, because it is an ongoing registry study, not all patients who enrolled at the baseline have progressed into mid- to long-term follow-up. At last, no disease

recurrence data were available in the NCR which could have biased the levels of psychological distress and QoL [48]. The 3-year cumulative incidence of recurrences for stage I, II and III CRC is reported to be approximately 0.05, 0.17 and 0.31, respectively [48]. The highest recurrence risk for stage III disease could explain the lower QoL patient group wherein recurrences and their possible subsequent treatments might have influenced patients' health status.

In conclusion, most patients treated for stage I–III CRC did well and reported high HR-QoL, low symptom burden and low psychological distress. A small but significant proportion of around 13% did not recover during follow-up and reported low HR-QoL or high psychological distress levels throughout. Female gender, younger age, lower educational level and major LARS were risk factors for belonging to this poor performing patient group. Future longitudinal studies should also consider investigating psychological variables as determinants in trajectory analyses. Besides focussing on risk of disease recurrence, future changes in follow-up should also incorporate sociodemographic and patient-reported outcome measures when personalising CRC follow-up.

Author contributions

Study concepts: SQ, JdW, JC.
Study design: SQ, JdW, RV, JC.
Data acquisition: SQ, RV, JH.
Quality control of data and algorithms: SQ, JH, RV, JdW, JC.
Data analysis and interpretation: SQ, JH, RV, JdW, JC.
Statistical analysis: SQ. JH, RV, JC.
Manuscript preparation: SQ, JH, RV, JdW, JC.
Manuscript editing: SQ, JH, RV, JdW, JC.
Manuscript review: SQ, JH, RV, JdW, JC.

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Conflict of interest statement

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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.2021.08.050.

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