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ORIGINAL ARTICLE

The relationship between systemic inflammatory response, screen detection and outcome in colorectal cancer

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Abstract

Aim: A raised systemic inflammatory response correlates with poorer colorectal cancer (CRC) outcomes. Faecal immunochemical test bowel screening aims to detect early-stage disease. We assessed the relationship between systemic inflammatory response, screen detection and CRC survival.

Method: A retrospective, observational cohort study compared screen-detected and non-screen-detected CRC patients undergoing resection. Systemic inflammatory response was measured using lymphocyte/monocyte, neutrophil/lymphocyte and platelet/lymphocyte ratios (LMR, NLR, PLR). Covariables were compared using χ^2 testing and survival with Cox regression.

Results: A total of 761 patients were included (326 screen-detected, 435 non-screen-detected). Screen-detected patients had lower systemic inflammatory response: low (<2.4) LMR (28.8% vs. 44.6%; $P<0.001$), moderate (3–5) or high (>5) NLR (26.1% vs. 30.6%, $P<0.001$; and 7.7% vs. 19.5%, $P<0.001$) and high (>150) PLR (47.2% vs. 64.6%; $P<0.001$). Median follow-up was 63 months. On univariate analysis, non-screen detection (hazard ratio [HR] 2.346, 95% CI 1.687–3.261; $P<0.001$), advanced TNM ($P<0.001$), low LMR (HR 2.038, 95% CI 1.514–2.742; $P<0.001$), moderate NLR (HR 1.588, 95% CI 1.128–2.235; $P=0.008$), high NLR (HR 2.382, 95% CI 1.626–3.491; $P<0.001$) and high PLR (HR 1.827, 95% CI 1.326–2.519; $P<0.001$) predicted poorer overall survival (OS). Non-screen detection (HR 2.713, 95% CI 1.742–4.226; $P<0.001$), TNM ($P<0.001$), low LMR (HR 1.969, 95% CI 1.340–2.893; $P<0.001$), high NLR (HR 2.368, 95% CI 1.448–3.875; $P<0.001$) and high PLR (HR 2.110, 95% CI 1.374–3.240; $P<0.001$) predicted poorer cancer-specific survival (CSS). On multivariate analysis, non-screen detection (HR 1.698, 95% CI 1.152–2.503; $P=0.008$) and low LMR (HR 1.610, 95% CI 1.158–2.238; $P=0.005$) independently predicted poorer OS. Non-screen detection (HR 1.847, 95% CI 1.144–2.983; $P=0.012$) and high PLR (HR 1.578, 95% CI 1.018–2.444; $P=0.041$) predicted poorer CSS.

This study was reported according to STROBE guidelines.

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Caldicott Guardian approval was given by NHS GG&C to safeguard the record linkage with ethical approval waived for the purposes of service development.

Conclusion: Screen-detected CRC patients have a lower systemic inflammatory response. Non-screen detection and systemic inflammatory response (measured by LMR and PLR respectively) were independent predictors of poorer OS and CSS.

KEYWORDS
cancer, colorectal, inflammation, screening, SIR

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer in the UK, with approximately 43 000 new cases and 16 500 deaths each year [1]. The Scottish Bowel Screening Programme invites patients aged 50–74 years to undertake a quantitative faecal immunochemical test (FIT) followed by colonoscopy for those testing positive (threshold 80 μg Hb/g faeces) [2]. This approach to screening increases the number of early-stage cancers diagnosed and reduces cancer-specific mortality [3–6]. Those who undergo resection have lower T staging and less evidence of adverse pathological features such as venous invasion, peritoneal and margin involvement [7–9]. Additionally, there are some data that the incidence of CRC may be reduced within a screened population through the removal of pre-malignant polyps [6].

As well as demonstrating improved outcomes with screening, it is also important to understand the inherent host-factor differences that exist between the screen-detected and non-screen-detected populations. Previous studies have shown that screen-detected patients are more likely to be men, younger, less socioeconomically deprived and have a lower systemic inflammatory response [7–9]. The presence of an elevated systemic inflammatory response is known to be associated with an adverse outcome after a diagnosis of CRC. Further work is required to determine the impact of an elevated systemic inflammatory response on outcomes within the Scottish Bowel Screening Programme. The aim of this study was to assess the relationship between systemic inflammatory response, screen detection and overall survival (OS) and cancer-specific survival (CSS) in patients with CRC.

What does this paper add to the literature?

We have established that screen-detected colorectal cancer patients have lower systemic inflammatory response compared to non-screen-detected patients. This is the first paper to measure systemic inflammatory response in such patients using lymphocyte/monocyte, neutrophil/lymphocyte and platelet/lymphocyte ratios. Additionally, systemic inflammatory response was shown to predict overall survival and cancer-specific survival, independent of screening status.

METHOD

Study design, setting and participants

A retrospective observational cohort study was conducted. The cohort was formed from all patients invited to the first complete round of the Scottish Bowel Screening Programme in National Health Service Greater Glasgow and Clyde (NHS GG&C) between April 2009 and March 2011, whether they participated in screening or not. Patients were only included if they were diagnosed with a CRC and underwent resection with curative intent within 2 years of their screening invitation. Patients were classified as those diagnosed with CRC directly through Scottish Bowel Screening Programme participation (screen-detected patients) or via symptomatic pathways (non-screen-detected patients). In Scotland, colonoscopy is only routinely performed in asymptomatic individuals within the Scottish Bowel Screening Programme and so all non-screen-detected patients were scoped via symptomatic referral pathways. Approval for this study was given by the Caldicott Guardian of the screening dataset and by the West of Scotland CRC Managed Clinical Network Management Group. Ethical approval and individual patient consent were waived as the study was entirely retrospective, observational and anonymized and the study was performed in accordance with the Declaration of Helsinki. The results have been reported according to STROBE guidelines [10].

Variables and data sources

The formation of this cohort has been previously described [8]. Briefly, details of all individuals invited to the first complete round of the Scottish Bowel Screening Programme in NHS GG&C between April 2009 and March 2011 were extracted from a prospectively maintained database. To ensure identification of both screen-detected patients and patients with non-screen-detected CRC diagnosed during the same period, the West of Scotland CRC Managed Clinical Network and Scottish Cancer Registry (SMR06) datasets were cross-referenced. Baseline demographics, preoperative blood results and survival were obtained on a case-by-case basis from NHS electronic patient records.

The presence of a systemic inflammatory response was quantified using three previously validated scores, the lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR). These scores are derived from circulating lymphocyte, monocyte, neutrophil and platelet counts, taken from

a preoperative full blood count. In each case the ratios were calculated by dividing the former by the latter. A greater systemic inflammatory response is associated with a lower LMR and a higher NLR or PLR. Thresholds were derived from previously published data [11]: low LMR <2.4, high LMR ≥2.4; low NLR <3, moderate NLR 3–5, high NLR >5; low PLR ≤150, high PLR >150. Deprivation was quantified using the Scottish Index of Multiple Deprivation, derived from each patient's post code. The Scottish Index of Multiple Deprivation is a measure of an area's deprivation based on income, employment, education, health, access to services, crime and housing [12]. Comorbidity was quantified using the American Society of Anesthesiologists (ASA) score and the Lee index [13]. Patients were excluded from the final analysis if their records were absent from the NHS electronic patient record system or if preoperative blood results were unavailable.

Data analysis and statistical methods

Covariables were compared using crosstabulation and the χ^2 test for linear trend. A value of $P<0.05$ was considered statistically significant. OS and CSS were analysed using Cox regression. All covariables found to be statistically significant ($P<0.05$) predictors of survival on univariate analysis were carried forward to a multivariate survival analysis. To reduce the impact of collinearity between explanatory variables, a stepwise backward method was used to produce a final model of variables with a significant independent impact on survival, where variables were removed from the model when the corresponding P value was >0.05. This statistical analysis was performed using SPSS software (SPSS Inc.).

RESULTS

Participants

Of all 395 097 patients invited to participate in the first complete round of screening in NHS GG&C, 204 535 (51.7%) responded of whom 6159 (3.0%) tested positive. Of those testing positive, 4797 (77.9%) proceeded to colonoscopy and 421 (8.8%) of those patients were found to have CRC. There were 708 patients with non-screen-detected CRCs diagnosed in NHS GG&C during the same time period of whom 468 (66.1%) were non-responders to screening, 182 (25.7%) were interval cancers (within 2 years of a negative screening test), 43 (6.1%) were individuals who chose not to attend colonoscopy following a positive screening FIT test and 15 (2.1%) had no malignancy detected at index screening colonoscopy. Of the 1129 total (421 screen-detected and 708 non-screen-detected), 761 patients underwent a surgical resection with curative intent, had complete NHS electronic portal records including preoperative blood results and were included in the final analysis. 326 (42.8%) of these patients had screen-detected and 435 (57.2%) had non-screen-detected disease (Figure 1). Of the 435 non-screen-detected patients, 269

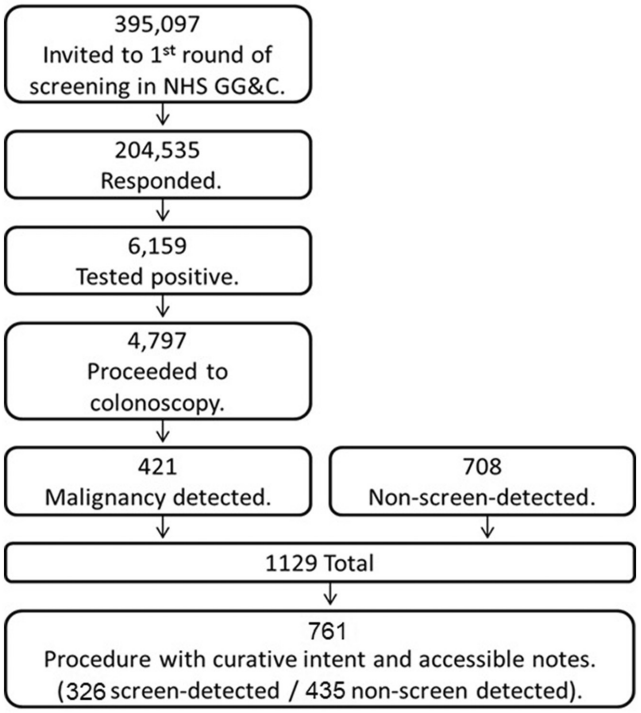


FIGURE 1 Flowchart of patient identification.

(61.8%) were non-responders, 125 (28.7%) were interval cancers, 29 (6.7%) refused colonoscopy following a positive FIT test and 12 (2.8%) had a normal index screening colonoscopy.

Systemic inflammatory response

Examining the three measures of systemic inflammatory response, screen-detected patients were less likely to have evidence of a raised systemic inflammatory response as measured by a low LMR (28.8% vs. 44.6%; $P<0.001$), a moderate or high NLR (26.1% vs. 30.6%, $P<0.001$; and 7.7% vs. 19.5%, $P<0.001$) and a high PLR (47.2% vs. 64.6%; $P<0.001$).

Demographics

Of all 761 patients included in the study, the median age at time of resection was 67 years (range 50–77); 452 (59.4%) were men and 309 (40.6%) were women. TNM distribution was Stage I 233 (30.6%), II 261 (34.3%), III 229 (30.1%), IV 38 (5.0%). Twenty-seven (3.5%) patients had synchronous tumours; 247 (32.5%) had rectal cancer, 512 (67.3%) colonic and two (0.3%) had synchronous colonic and rectal tumours. 473 (62.2%) patients had a raised systemic inflammatory response based on a low LMR, 328 (43.1%) based on a moderate or high NLR and 435 (57.2%) based on a high PLR.

A comparison of demographics between screen-detected and non-screen-detected patients can be seen in Table 1. Patients with screen-detected disease were significantly more likely to be

TABLE 1 Baseline demographics and comparison of patients with screen-detected and non-screen-detected colorectal cancer.

	All patients *n* (%)	Screen-detected *n* (%)	Non-screen-detected *n* (%)	*P* value
Age, years				
≤62	250 (32.9%)	100 (30.7%)	150 (34.5%)	
63–70	252 (33.1%)	118 (36.2%)	134 (30.8%)	
≥71	259 (34.0%)	108 (33.1%)	151 (34.7%)	0.273
Sex				
Male	452 (59.4%)	211 (64.7%)	241 (55.4%)	
Female	309 (40.6%)	115 (35.3%)	194 (44.6%)	0.01
Deprivation				
Non-deprived (SIMD 3–5)	371 (48.8%)	175 (53.7%)	196 (45.1%)	
Deprived (SIMD 1–2)	390 (51.2%)	151 (46.3%)	239 (54.9%)	0.019
Presentation				
Elective	687 (90.3%)	324 (99.4%)	363 (83.4%)	
Emergency	74 (9.7%)	2 (0.6%)	72 (16.6%)	<0.001
Tumour site[a]				
Colon	512 (67.5%)	239 (73.3%)	273 (63.0%)	
Rectum	247 (32.5%)	87 (26.7%)	160 (37.0%)	0.003
TNM stage				
1	233 (30.6%)	129 (39.6%)	104 (23.9%)	
2	261 (34.3%)	90 (27.6%)	171 (39.3%)	
3	229 (30.1%)	97 (29.8%)	132 (30.3%)	
4	38 (5.0%)	10 (3.1%)	28 (6.4%)	<0.001
T stage				
1	136 (17.9%)	89 (27.3%)	47 (10.8%)	
2	123 (16.2%)	59 (18.1%)	64 (14.7%)	
3	362 (47.6%)	151 (46.3%)	211 (48.5%)	
4	140 (18.4%)	27 (8.3%)	113 (26.0%)	<0.001
N stage				
0	496 (65.2%)	223 (68.4%)	273 (62.8%)	
1	177 (23.3%)	70 (21.5%)	107 (24.6%)	
2	88 (11.6%)	33 (10.1%)	55 (12.6%)	0.257
ASA score[b]				
Low (1, 2)	433 (66.6%)	191 (72.6%)	242 (62.5%)	
High (≥3)	217 (33.4%)	72 (27.4%)	145 (37.5%)	0.007
Lee index				
Low	612 (80.4%)	273 (83.7%)	339 (77.9%)	
High	149 (19.6%)	53 (16.3%)	96 (22.1%)	0.046
LMR				
High (≥2.4)	473 (62.2%)	232 (71.2%)	241 (55.4%)	
Low (<2.4)	288 (37.8%)	94 (28.8%)	194 (44.6%)	<0.001
NLR				
Low (<3)	433 (56.9%)	216 (66.3%)	217 (49.9%)	
Moderate (3–5)	218 (28.6%)	85 (26.1%)	133 (30.6%)	
High (>5)	110 (14.5%)	25 (7.7%)	85 (19.5%)	<0.001
PLR				
Low (≤150)	326 (42.8%)	172 (52.8%)	154 (35.4%)	
High (>150)	435 (57.2%)	154 (47.2%)	281 (64.6%)	<0.001

Abbreviations: ASA, American Society of Anesthesiologists; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIMD, Scottish Index of Multiple Deprivation.

[a]Two (0.3%) patients were not included in this comparison as they had synchronous colonic and rectal tumours.

[b]Data missing for 111 (14.6%) patients.

men (64.7% vs. 55.4%; $P=0.01$), less deprived (46.3% vs. 54.9%; $P=0.019$), have a significantly lower rate of emergency presentations (0.6% vs. 9.7%; $P<0.001$), a higher rate of colonic tumours (73.3% vs. 63.0%; $P=0.003$), an earlier TNM stage ($P<0.001$), in particular T stage ($P<0.001$), and were less comorbid based on the ASA score ($P=0.007$) and Lee index ($P=0.046$).

Survival

With a median follow-up of 63 months (range 33–83 months), 184 (24.2%) patients died of whom 105 (57.1%) patients died of CRC. Eight (1.1%) died within 30 days of their operation (four screen-detected, four non-screen-detected). For the whole cohort, 5-year OS was 77.3% and 5-year CSS was 85.3%. For screen-detected patients, 5-year OS and CSS were 86.0% and 92.1%, compared with 70.0% and 79.7% respectively for non-screen-detected patients.

Tables 2 and 3 display the outcomes of both univariate and multivariate survival analysis for OS and CSS respectively. Excluding postoperative deaths, on univariate analysis non-screen detection (hazard ratio [HR] 2.346, 95% CI 1.687–3.261; $P<0.001$) (Figure 2), emergency presentation (HR 3.383, 95% CI 2.358–4.853; $P<0.001$), advanced TNM stage (III or IV) ($P<0.001$) (Figure 3), high (≥3) ASA score (HR 1.818, 95% CI 1.320–2.505; $P<0.001$), low (<2.4) LMR (HR 2.038, 95% CI 1.514–2.742; $P<0.001$) (Figure 4), moderate [3–5] NLR (HR 1.588, 95% CI 1.128–2.235; $P=0.008$), high (>5) NLR (HR 2.382, 95% CI 1.626–3.491; $P<0.001$) (Figure 5) and high (>150) PLR (HR 1.827, 95% CI 1.326–2.519; $P<0.001$) (Figure 6) were all associated with poorer OS. Excluding postoperative deaths, non-screen detection (HR 2.713, 95% CI 1.742–4.226; $P<0.001$), emergency presentation (HR 5.128, 95% CI 3.364–7.817; $P<0.001$), advanced TNM stage (III or IV) ($P<0.001$), low (<2.4) LMR (HR 1.969, 95% CI 1.340–2.893; $P<0.001$), high (>5) NLR (HR 2.368, 95% CI 1.448–3.875; $P<0.001$) and high (>150) PLR (HR 2.110, 95% CI 1.374–3.240; $P<0.001$) were also associated with poorer CSS.

On multivariate analysis non-screen detection (HR 1.698, 95% CI 1.152–2.503; $P=0.008$), emergency presentation (HR 1.879, 95% CI 1.228–2.875; $P=0.004$), advanced TNM stage (III or IV) ($P<0.001$) and low LMR (HR 1.610, 95% CI 1.158–2.238; $P=0.005$) retained significance as independent predictors of OS. Non-screen detection (HR 1.847, 95% CI 1.144–2.983; $P=0.012$), emergency presentation (HR 2.399, 95% CI 1.507–3.820; $P<0.001$), advanced TNM stage (III or IV) ($P<0.001$) and PLR (HR 1.578, 95% CI 1.018–2.444; $P=0.041$) retained significance as independent predictors of CSS.

DISCUSSION

In the current study we have established that patients with screen-detected CRC have a significantly lower systemic inflammatory response compared to their non-screen-detected counterparts, as quantified by LMR, NLR and PLR. This is the first study to compare the systemic inflammatory response between screen-detected and non-screen-detected CRC patients, using all three of these validated markers. Additionally, we have shown that a raised systemic inflammatory response as measured by LMR is associated with poorer OS, and a raised systemic inflammatory response as measured by PLR is associated with poorer CSS, independent of screening status.

A plethora of evidence has linked poorer prognosis in CRC with the presence of a raised systemic inflammatory response. A heightened systemic inflammatory response is associated with adverse prognostic features including higher TNM staging [14, 15], poorly differentiated tumours [11, 14, 15], the presence of venous invasion [11, 14], perineural invasion [16], peritoneal involvement [11, 14], margin involvement [11, 14], emergency presentation [15] and tumour perforation [11, 14]. Furthermore, a raised systemic inflammatory response has been shown to independently predict OS and CSS in patients with both primary resectable [11, 14–23] and metastatic CRC [24–28], including in large systematic reviews and meta-analyses [29–33].

It has been well established that patients with screen-detected CRC have improved outcomes compared to their non-screen-detected counterparts [3–9]. Earlier stage of presentation is certainly a key determinant of these improved outcomes. For example, in the current study we have shown that patients with screen-detected disease have significantly lower TNM staging and fewer emergency operations than those with non-screen-detected disease. Additionally, previous work has shown that screen-detected patients undergoing resection have less venous invasion and less peritoneal and margin involvement [7, 8]. However, as can be seen in Figure S1A,B, screen-detected patients in this study had improved OS and CSS regardless of stage at diagnosis. There are several inherent differences between screen-detected and non-screen-detected patients which may also contribute to improved outcome. In the current study, screen-detected patients were more likely to be men, less deprived, less comorbid and have fewer rectal cancers. The systemic inflammatory response is one host factor that to date has not been studied in detail in relation to screen-detected versus non-screen-detected disease. Previous studies on the current cohort of patients have revealed a higher systemic inflammatory response as measured by NLR [8, 34]. In the current study we decided to expand our investigation by using three validated markers of systemic inflammatory response (LMR, NLR and PLR) and by performing multivariate survival analysis. All three markers showed significantly less systemic inflammation amongst screen-detected patients. Additionally, for the first time, on multivariate survival analysis LMR was able to independently predict OS and PLR was able to predict CSS. Simultaneously, screen detection retained significance as an independent predictor of both OS and CSS. We can therefore conclude that screen-detected patients have less systemic inflammation and that, along with other screen-detected benefits including earlier staging at diagnosis, less deprivation and lower comorbidity, this may be one factor which contributes to the improved outcomes seen within this group. However, while there is a relationship between screen detection and a lower systemic inflammatory response, it is important to note that both represent independent and valuable

TABLE 2 Factors associated with overall survival in patients with colorectal cancer undergoing resection with a curative intent.

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years						
<62	1.0					
63–70	1.068	0.729–1.563	0.736			
≥71	1.325	0.921–1.905	0.129			
Sex						
Male	1.0					
Female	0.999	0.737–1.354	0.995			
Screen detected						
Yes	1.0			1.0		
No	2.346	1.687–3.261	<0.001	1.698	1.152–2.503	0.008
SIMD						
Non-deprived (1, 2)	1.0					
Deprived (3–5)	1.211	0.899–1.632	0.207			
Presentation						
Elective	1.0			1.0		
Emergency	3.383	2.358–4.853	<0.001	1.879	1.228–2.875	0.004
Tumour site						
Colon	1.0					
Rectum	1.020	0.745–1.397	0.900			
TNM stage						
I	1.0			1.0		
II	1.545	0.979–2.438	0.62	1.136	0.679–1.902	0.628
III	2.681	1.746–4.116	<0.001	2.310	1.436–3.714	<0.001
IV	9.278	5.530–15.566	<0.001	6.716	3.777–11.945	<0.001
ASA score						
Low (1, 2)	1.0			1.0		
High (≥3)	1.818	1.320–2.505	<0.001	1.369	0.980–1.912	0.065
Lee index						
Low	1.0					
High	1.316	0.926–1.870	0.125			
LMR						
High (≥2.4)	1.0			1.0		
Low (<2.4)	2.038	1.514–2.742	<0.001	1.610	1.158–2.238	0.005
NLR						
Low (<3)	1.0			1.0		
Moderate (3–5)	1.588	1.128–2.235	0.008	0.971	0.625–1.508	0.895
High (>5)	2.382	1.626–3.491	<0.001	0.646	0.368–1.135	0.129
PLR						
Low (≤150)	1.0			1.0		
High (>150)	1.827	1.326–2.519	<0.001	1.474	0.993–2.190	0.054

Abbreviations: ASA, American Society of Anesthesiologists; HR, hazard ratio; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIMD, Scottish Index of Multiple Deprivation.

TABLE 3 Factors associated with cancer-specific survival in patients with colorectal cancer undergoing resection with a curative intent.

	Univariate			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years						
<62	1.0					
63–70	0.811	0.505–1.303	0.386			
≥71	0.913	0.577–1.444	0.696			
Sex						
Male	1.0					
Female	1.064	0.720–1.572	0.755			
Screen detected						
Yes	1.0			1.0		
No	2.713	1.742–4.226	<0.001	1.847	1.144–2.983	0.012
SIMD						
Non-deprived (1, 2)	1.0					
Deprived (3–5)	1.004	0.684–1.475	0.983			
Presentation						
Elective	1.0			1.0		
Emergency	5.128	3.364–7.817	<0.001	2.399	1.507–3.820	<0.001
Tumour site						
Colon	1.0					
Rectum	1.229	0.801–1.886	0.345			
TNM stage						
I	1.0			1.0		
II	2.145	0.976–4.710	0.057	1.533	0.689–3.410	0.295
III	6.440	3.163–13.113	<0.001	4.884	2.374–10.049	<0.001
IV	29.783	13.923–63.711	<0.001	19.917	9.099–43.594	<0.001
ASA score						
Low (1, 2)	1.0					
High (≥3)	1.326	0.871–2.021	0.189			
Lee index						
Low	1.0					
High	1.249	0.786–1.984	0.347			
LMR						
High (≥2.4)	1.0			1.0		
Low (<2.4)	1.969	1.340–2.893	<0.001	1.527	0.906–2.574	0.112
NLR						
Low (<3)	1.0			1.0		
Moderate (3–5)	1.513	0.969–2.361	0.068	0.853	0.487–1.494	0.579
High (>5)	2.368	1.448–3.875	<0.001	0.664	0.340–1.298	0.231
PLR						
Low (≤150)	1.0			1.0		
High (>150)	2.110	1.374–3.240	<0.001	1.578	1.018–2.444	0.041

Abbreviations: ASA, American Society of Anesthesiologists; HR, hazard ratio; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIMD, Scottish Index of Multiple Deprivation.

prognostic markers. In Figure S2A,B it can be seen that screen-detected patients had improved OS and CSS, whether they had high or low systemic inflammation as measured by LMR. Therefore, measures of the systemic inflammatory response remain valid predictors of survival in screen-detected patients as well as non-screen-detected patients. Additionally, further work is required to refine

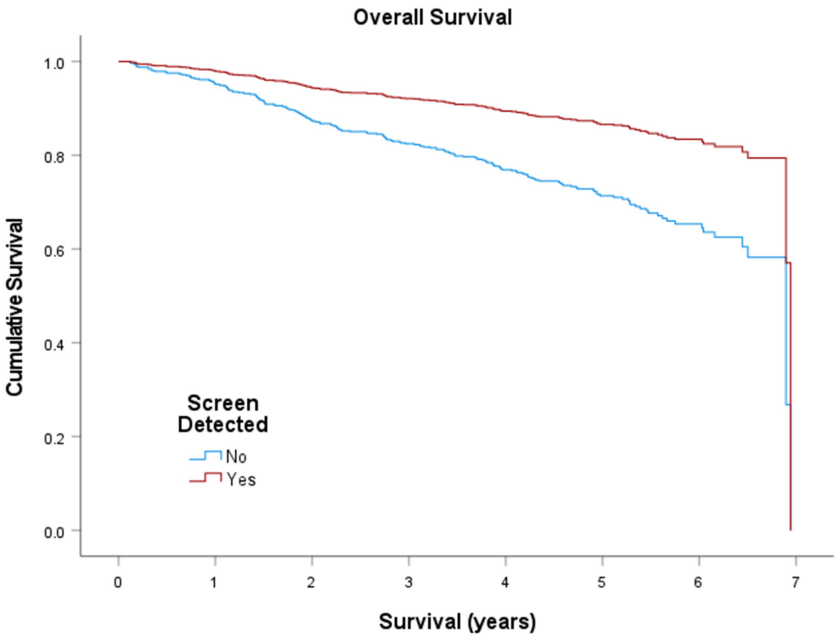
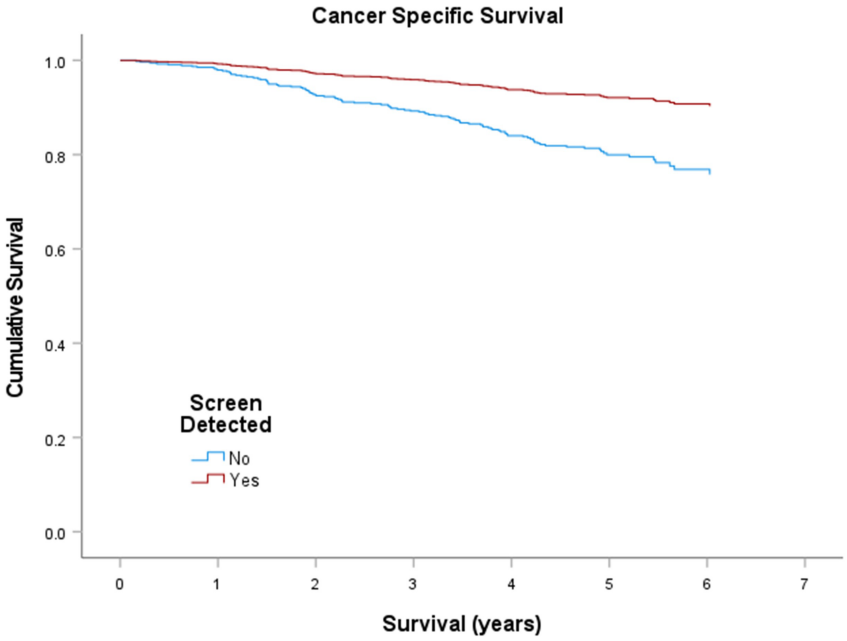


FIGURE 2 Relationship between screen detection and OS and CSS.

Number at Risk

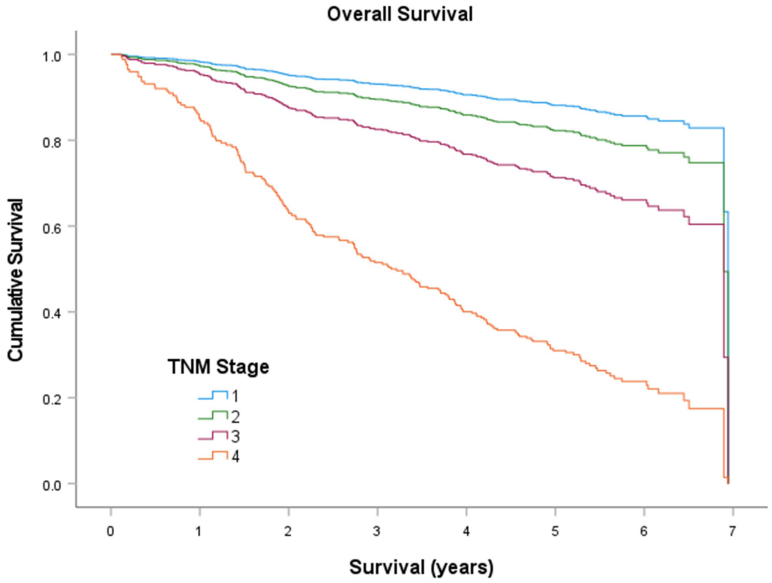
NSD	431	410	377	326	217	92	21
SD	322	316	304	297	255	160	49



Number at Risk

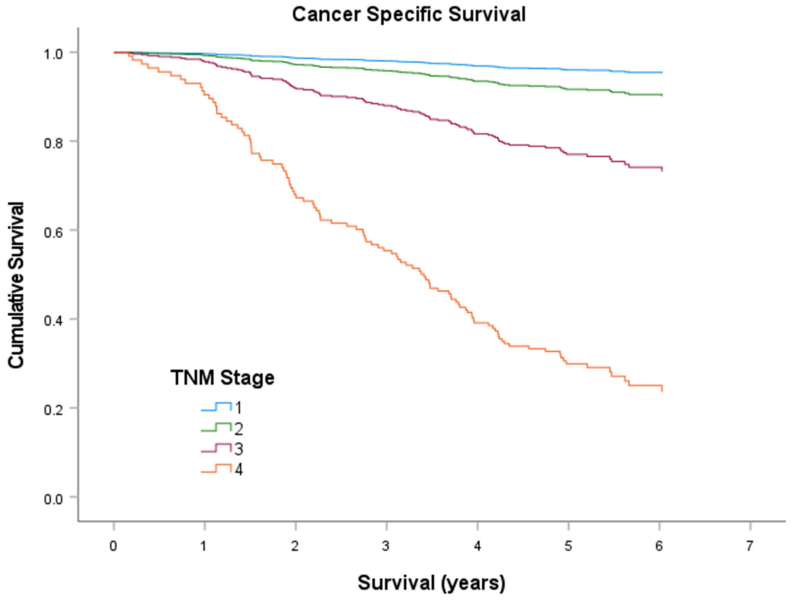
NSD	426	404	373	324	214	90	20
SD	319	314	302	296	254	158	47

FIGURE 3 Relationship between TNM stage and OS and CSS.



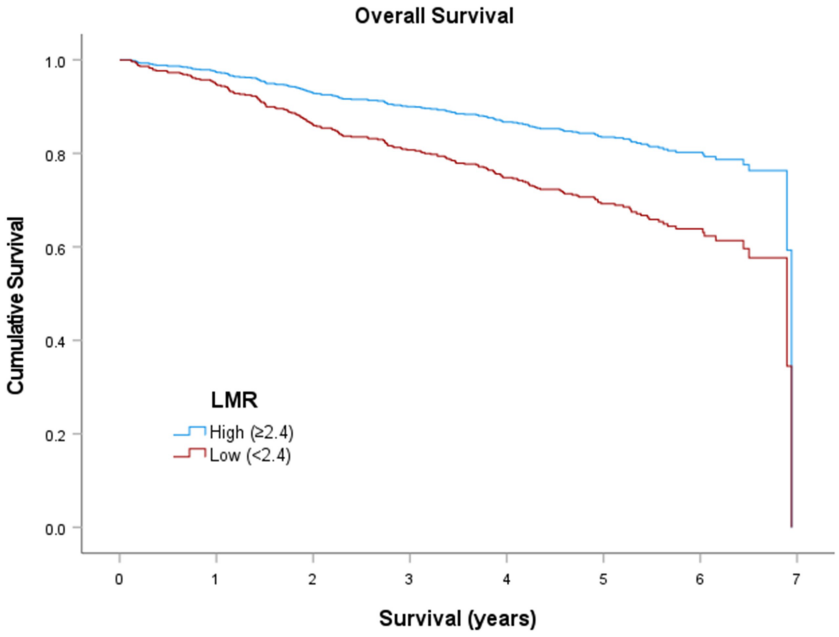
Number at Risk

Stage I	231	227	223	211	167	89	25
Stage II	258	249	237	218	164	89	23
Stage III	226	218	196	174	130	67	20
Stage IV	38	32	25	20	12	7	2



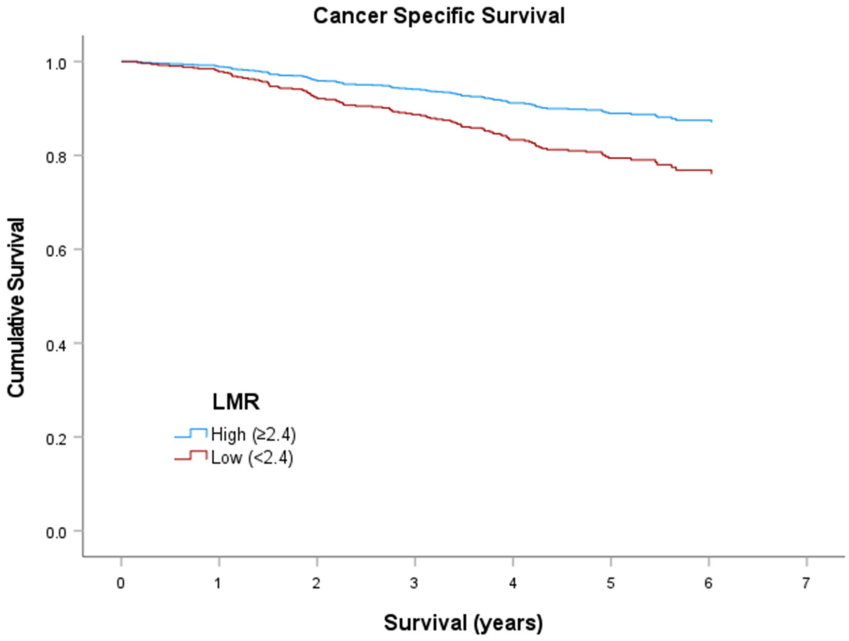
Number at Risk

Stage I	229	226	221	210	165	87	24
Stage II	254	247	236	216	163	87	22
Stage III	225	213	194	174	129	67	20
Stage IV	38	32	25	20	11	7	2



Number at Risk

High	470	460	446	410	315	171	46
Low	283	266	235	213	158	81	24



Number at Risk

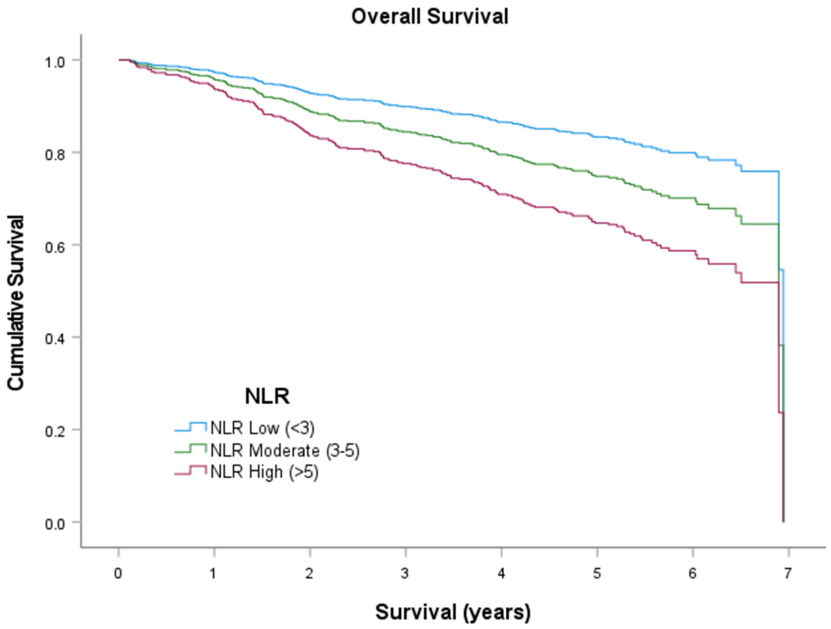
Low	467	458	442	408	312	168	45
High	278	260	233	212	156	80	22

FIGURE 4 Relationship between LMR and OS and CSS.

the inherent differences between screen-detected and non-screen-detected patients, in terms of both host and tumour factors.

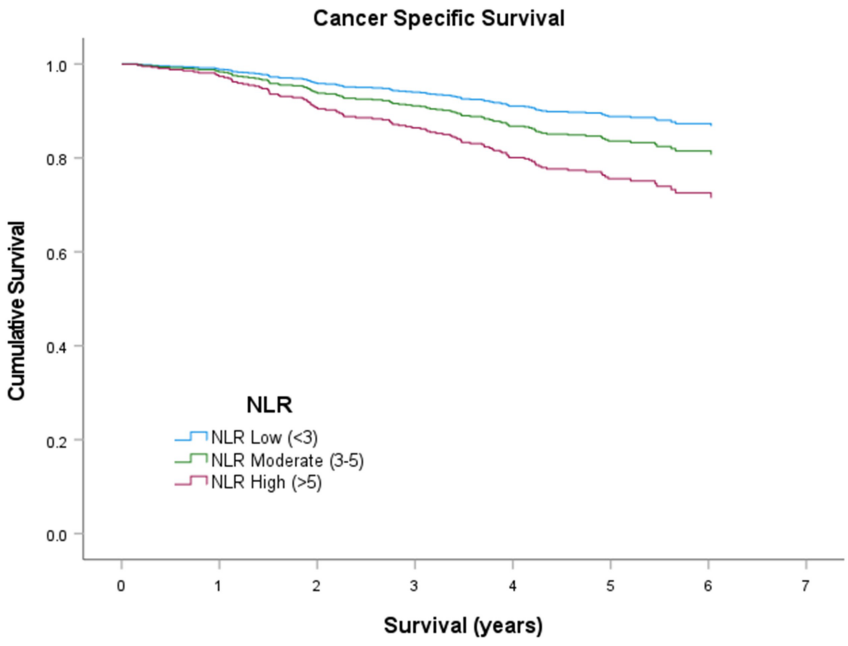
The present study has several strengths. We have been able to form a comprehensive cohort of both screen-detected and non-screen-detected CRC patients diagnosed during the study period, within our health board. Access to Scottish Bowel Screening Programme data allowed the identification of all screen-detected patients, while the use of cancer registries ensured capture of

FIGURE 5 Relationship between NLR and OS and CSS.



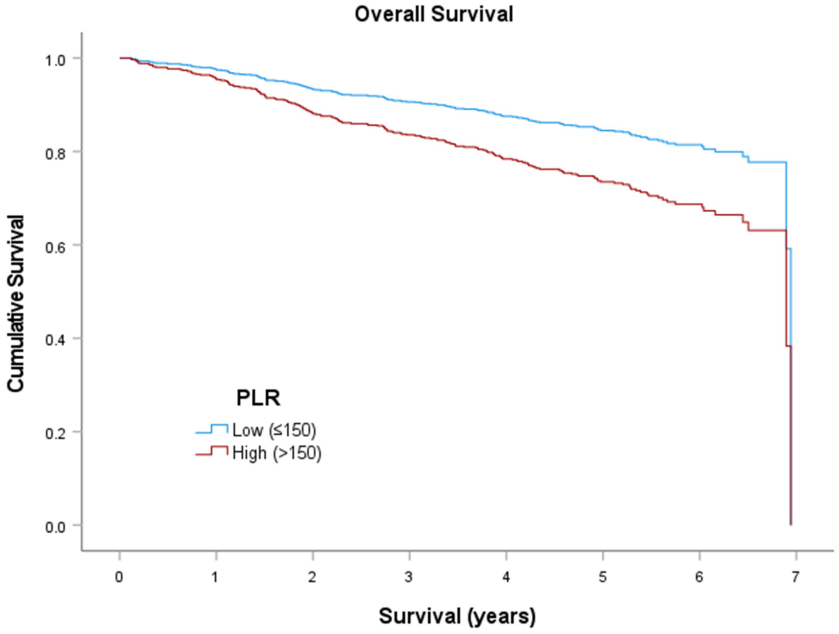
Number at Risk

Low	430	419	404	371	284	155	45
Moderate	216	204	188	172	131	73	20
High	107	103	89	80	58	25	5



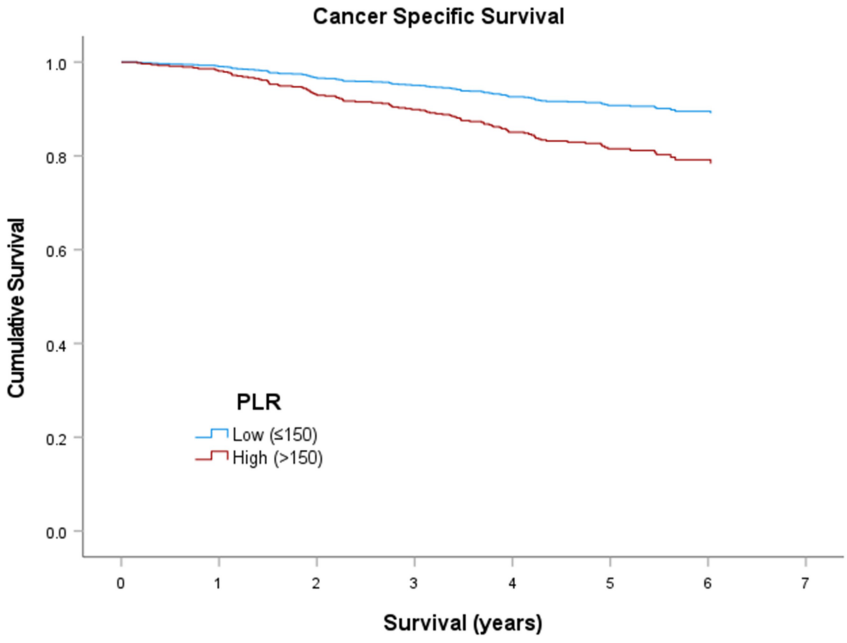
Number at Risk

Low	427	417	400	370	282	152	43
Moderate	212	201	187	171	130	72	20
High	106	100	89	80	57	24	4



Number at Risk

Low	322	315	302	280	216	120	34
High	431	411	379	343	256	132	36



Number at Risk

Low	320	313	299	279	214	119	33
High	425	405	376	341	254	129	34

FIGURE 6 Relationship between PLR and OS and CSS.

non-screen-detected patients diagnosed via symptomatic pathways at the same time. This is the first study to compare the systemic inflammatory response between screen-detected and non-screen-detected patients using a broad panel of markers (LMR, NLR and PLR). By performing multivariate survival analysis with a long median follow-up of 63 months and with an extensive

list of covariables, we have been able to establish the impact of systemic inflammatory response on outcomes in the Scottish Bowel Screening Programme. Limitations of the study include its retrospective nature such that an ASA score was missing for 14.6% of patients, and participants without record of a preoperative full blood count for the purposes of calculating LMR, NLR and PLR were excluded. The modified Glasgow Prognostic Score is another widely validated measure of systemic inflammatory response that utilizes C-reactive protein and albumin levels, a positive and a negative acute phase reactant protein respectively. Unfortunately, we were unable to include this measure due to lack of data. Additionally, while we have tried to account for potential confounding by performing multivariate analysis, the included list of covariables is not exhaustive and missing information, notably smoking status, has not been accounted for. Finally, the effect of lead-time bias, where earlier detection artificially lengthens a patient's survival following a cancer diagnosis, has not been considered. However, adjusting for this confounder within the context of a retrospective cohort study is complex and beyond the scope of the present study.

CONCLUSIONS

Patients with screen-detected CRC have a lower systemic inflammatory response than those with non-screen-detected disease as measured by LMR, NLR and PLR. Despite this, after adjusting for a broad range of covariables, both screen detection and a raised systemic inflammatory response as measured by LMR and PLR retained significance as independent predictors of poorer OS and CSS respectively. Further work is required to refine the inherent differences between screen-detected and non-screen-detected patients with regard to the systemic inflammatory response.

AUTHOR CONTRIBUTIONS

Mark S. Johnstone: Data curation; formal analysis; investigation; writing – original draft; methodology; validation. **Steven T. McSorley:** Supervision; writing – review and editing. **Donald McMillan:** Writing – review and editing; supervision. **Paul Horgan:** Writing – review and editing; supervision. **David Mansouri:** Writing – review and editing; conceptualization; methodology; data curation; supervision; investigation.

FUNDING INFORMATION

No funding was associated with this research.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

A completely anonymized version of the data used to complete this study is available upon request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval for this study was given by the Caldicott Guardian of the screening dataset and by the West of Scotland Colorectal Cancer Managed Clinical Network Management Group. Ethical approval and individual patient consent were waived as the study was entirely retrospective, observational and anonymized and the study was performed in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All authors give their consent for publication.

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REFERENCES

1. Cancer Research UK. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer
2. Scottish Bowel Screening Programme—a guide for professionals. Available from: http://www.healthscotland.scot/publications/scottish-bowel-screening-programme-a-guide-for-professionals
3. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota colon cancer control study. N Engl J Med. 1993;328(19):1365–71.
4. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472–7.
5. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467–71.
6. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007;2007(1):CD001216.
7. Mansouri D, McMillan DC, Grant Y, Crighton EM, Horgan PG. The impact of age, sex and socioeconomic deprivation on outcomes in a colorectal cancer screening programme. PLoS One. 2013;8(6):e66063-e.
8. Mansouri D, McMillan DC, McIlveen E, Crighton EM, Morrison DS, Horgan PG. A comparison of tumour and host prognostic factors in screen-detected vs nonscreen-detected colorectal cancer: a contemporaneous study. Colorectal Dis. 2016;18(10):967–75.
9. Morris EJ, Whitehouse LE, Farrell T, Nickerson C, Thomas JD, Quirke P, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. Br J Cancer. 2012;107(5):757–64.
10. Strengthening the reporting of observational studies in epidemiology. https://www.strobe-statement.org/ [cited 2023 April 04]. Available from: https://www.strobe-statement.org/
11. Dolan RD, McSorley ST, Park JH, Watt DG, Roxburgh CS, Horgan PG, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: comparison of composite ratios and cumulative scores. Br J Cancer. 2018;119(1):40–51.
12. Scottish Index of Multiple Deprivation. 2020 [cited 2021 Nov 08]. Available from: https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/
13. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043–9.

14. Park JH, Watt DG, Roxburgh CS, Horgan PG, McMillan DC. Colorectal cancer, systemic inflammation, and outcome: staging the tumor and staging the host. Ann Surg. 2016;263(2):326–36.
15. Park JH, Fuglestad AJ, Køstner AH, Oliwa A, Graham J, Horgan PG, et al. Systemic inflammation and outcome in 2295 patients with stage I–II colorectal cancer from Scotland and Norway: first results from the ScotScan colorectal cancer group. Ann Surg Oncol. 2020;27(8):2784–94.
16. Jakubowska K, Koda M, Grudzińska M, Kańczuga-Koda L, Famulski W. Monocyte-to-lymphocyte ratio as a prognostic factor in peripheral whole blood samples of colorectal cancer patients. World J Gastroenterol. 2020;26(31):4639–55.
17. McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr. 2018;37(4):1279–85.
18. McSorley ST, Johnstone M, Steele CW, Roxburgh CSD, Horgan PG, McMillan DC, et al. Normocytic anaemia is associated with systemic inflammation and poorer survival in patients with colorectal cancer treated with curative intent. Int J Colorectal Dis. 2019;34(3):401–8.
19. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):111–22.
20. Mazaki J, Katsumata K, Kasahara K, Tago T, Wada T, Kuwabara H, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: a propensity score analysis. BMC Cancer. 2020;20(1):922.
21. Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg. 2017;265(3):539–46.
22. Golder AM, McMillan DC, Park JH, Mansouri D, Horgan PG, Roxburgh CS. The prognostic value of combined measures of the systemic inflammatory response in patients with colon cancer: an analysis of 1700 patients. Br J Cancer. 2021;124(11):1828–35.
23. Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23(34):6261–72.
24. Køstner AH, Kersten C, Löwenmark T, Ydsten KA, Peltonen R, Isoniemi H, et al. The prognostic role of systemic inflammation in patients undergoing resection of colorectal liver metastases: C-reactive protein (CRP) is a strong negative prognostic biomarker. J Surg Oncol. 2016;114(7):895–9.
25. Li H, Liu Q, Liang S, Yao P, Lv J, Wang G, et al. Circulating tumor cells and neutrophil–lymphocyte ratio are predictive markers for metastatic colorectal cancer patients. Transl Cancer Res. 2021;10(1):288–97.
26. Verter E, Berger Y, Perl G, Peretz I, Tovar A, Morgenstern S, et al. Neutrophil-to-lymphocyte ratio predicts recurrence pattern in patients with resectable colorectal liver metastases. Ann Surg Oncol. 2021;28(8):4320–9.
27. Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Yamazoe S, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer. World J Gastroenterol. 2015;21(34):9966–73.
28. Gui W, Wang X, Luo Y, Wang J. Platelet to lymphocyte ratio as a prognostic factor in patients with advanced colorectal cancer undergoing palliative treatment. Ann Palliat Med. 2020;9(5):3271–7.
29. Tan D, Fu Y, Su Q, Wang H. Prognostic role of platelet–lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(24):e3837.
30. Wang J, Li J, Wei S, Xu J, Jiang X, Yang L. The ratio of platelets to lymphocytes predicts the prognosis of metastatic colorectal cancer: a review and meta-analysis. Gastroenterol Res Pract. 2021;2021:9699499.
31. Zhang J, Zhang H-Y, Li J, Shao X-Y, Zhang C-X. The elevated NLR, PLR and PLT may predict the prognosis of patients with colorectal cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(40):68837–46.
32. Rossi S, Basso M, Strippoli A, Schinzari G, D'Argento E, Larocca M, et al. Are markers of systemic inflammation good prognostic indicators in colorectal cancer? Clin Colorectal Cancer. 2017;16(4):264–74.
33. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. Int J Mol Sci. 2021;22(15):8002.
34. Johnstone MS, McMillan DC, Horgan PG, Mansouri D. The relationship between co-morbidity, screen-detection and outcome in patients undergoing resection for colorectal cancer. World J Surg. 2021;45(7):2251–60.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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