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Original Article

Age-Specific Socioeconomic Inequalities in Treatment in Patients with Stage III Colon Cancer in England 2012–2016: A Population-Based Study with Mediation Analysis

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Abstract

Aims: It is unclear whether inequalities in guidelines-recommended treatment among patients with stage III colon cancer existed and differed by age in England.

Materials and methods: Using data from cancer registry in England between 2012 and 2016, we included all patients with stage III colon cancer and applied multivariable multinominal logistic regression, including an interaction between age and deprivation, to investigate age-specific socioeconomic inequalities in receipt of the NICE-recommend treatment – surgery combined with adjuvant chemotherapy. We also examined the mediating roles of tumour factors on the inequalities in treatment.

Results: Among 20,368 included patients, socioeconomic inequalities in receipt of the NICE-recommend treatment were observed at all ages but wider in patients aged between 65 and 85 years old. For a 70-year-old patient, the probability of receiving the NICE-recommend treatment was 70.8% (95% CI: 68.6, 73.1) for the least vs. 59.4% (53.7, 65.1) for the most deprived quintile. When both groups were unlikely to receive the NICE-recommended treatment (85+ years old), patients from less deprived areas had a higher probability of receiving some alternative treatments like surgery while those with the most deprived backgrounds received none. Tumour factors explained little of inequalities in receipt of surgery or adjuvant chemotherapy.

Conclusion: Patients from deprived areas tended to receive inferior treatment options, and tumour factors explained little of these inequalities. Guidelines need to ensure that the NICE-recommended treatment modality is available to all to reduce the survival gap.

Key words: Adjuvant chemotherapy; age inequalities; colon cancer; mediation analysis; NICE-recommend treatment; socioeconomic inequalities; surgery

Introduction

Colon cancer is one of the most common cancers in England, with more than 23,000 cases diagnosed in 2017 and a quarter were diagnosed at stage III [1]. In a universal healthcare system like the National Health Service (NHS) in England, all patients should have equal access to treatments, but several studies have reported inequalities in a single treatment modality such as surgery [2] or adjuvant chemotherapy in stage II and/or III colorectal cancer [3–5]. The National Institute for Health and Care Excellence (NICE) recommends that patients with stage III colon cancer should receive a major resection with adjuvant chemotherapy, and inequalities might accumulate and multiply along the treatment pathway. Furthermore, these inequalities may differ by age as it is the key determinant of treatment [3,7].

Studies investigating inequalities in cancer in England often use the overall indices of multiple deprivation (IMD) [3,4,8,9] or the income domain of IMD [2,5,10–12] as the measures for deprivation. The first measure includes a domain of health deprivation and disability derived from morbidity, disability, and premature mortality at the Lower-layer Super Output Area (LSOA – mean population 1500) and is highly correlated with the outcome in public health research. The latter only considers the income aspect of socioeconomic status. The IMD research team indicates that it is possible to recreate alternative measures of deprivation at the LSOA level, based on different domains and/or

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weights than are used in the IMD [13]. To replicate a deprivation measure that is closer to the individual's material wealth, we could combine the three domains (i.e., income, education, and employment) that are more relevant for individuals, as other domains of IMD (i.e., crime, living environment, and barriers to housing and services) measure aspects related to the environment rather than residents.

In this study, we aimed to use a novel socioeconomic deprivation measure that captures individual aspects of socioeconomic status – a combination of income, education, and employment domains – to assess inequalities in receipt of the NICE-recommended treatment modalities, i.e., surgery combined with adjuvant chemotherapy. Furthermore, we will study how inequalities in treatment are modified by age and explained by tumour factors, to identify the most affected subgroups and the most actionable interventions.

Methods

Data Sources and Population

The National Cancer Registration and Analysis Service (NCRAS) database captures information on all primary cancer cases diagnosed in England, including patient sociodemographic factors, cancer characteristics and treatment [14]. At the patient level, this dataset was linked to Systemic Anti-Cancer Therapy (SACT) [15], and Hospital Episode Statistics Admitted Patient Care (HES APC) [16]. IMD measures the relative level of deprivation of 32,844 LSOAs in England [17], including seven domains: income (weights – 22.5%), employment (22.5%), education, skills and training (13.5%), health and disability (13.5%), crime (9.3%), barriers to housing and services (9.3%), and living environment (9.3%) [17]. NCRAS was linked to IMD 2015 dataset by the LSOA of the patient's residence when they were diagnosed.

We included a cohort of individuals aged between 18 and 90 years and with a primary diagnosis of stage III colon cancer (ICD-10: C18) in NCRAS between 1st January 2012 and 31st December 2016. Individuals with cancer information solely based on their death certificate were excluded from the study. We followed The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement in conducting and reporting this study [18].

Exposures, Outcomes, and Covariates

Our primary exposure was socioeconomic deprivation – created by including the three most individual-relevant domains, income, employment, and education skills and training, and following the methodology reported by the IMD research report [13]. We determined the weight of each domain by their relative contributions to the overall IMD, as if the deprivation only includes these three domains, i.e., Income (38.46%), Employment (38.46%), Education, Skills and Training (23.08%), and created quintiles of socioeconomic deprivation based on the national distribution of deprivation in 32,844 LSOAs. Individuals were assigned to a quintile according to the LSOA related to their residence at cancer diagnosis. We also analysed the three domains separately in sensitivity analyses.

The main outcome was the receipt of the NICE-recommended treatment, surgery followed by adjuvant chemotherapy [6] – this variable contained three categories: receipt of the NICE-recommended treatment, an alternative treatment modality if they received any treatment(s) other than the NICE-recommended combination, and no treatment at all. We used an outcome with three categories as some patients might not be fit for the NICE-recommended treatment – the Multidisciplinary Team deemed the risk (e.g., side effects or mortality) outweighs the benefit (e.g., survival gain), but it is still important to recognise that some alternative treatments were administered to treat cancer. Surgery was defined by the presence of procedure codes for bowel resections in HES APC or NCRAS within one year after the date of diagnosis [16]. Adjuvant chemotherapy was defined by the presence of chemotherapy records in NCRAS or SACT started within six months after the date of surgery [14,15]. We used a longer interval than recommended waiting time to capture treatment information as completely as possible; Figure S1 shows the intervals for these two modalities, indicating that more than 90% of surgeries and adjuvant chemotherapy were within three months after diagnosis and after surgery, respectively. As secondary outcomes, receipt of surgery in the study population and receipt of adjuvant chemotherapy in patients who received surgery were analysed separately to identify the source of inequalities, if any.

Sociodemographic factors included age at diagnosis, sex, and ethnicity (White or other ethnicities; a more detailed breakdown of other ethnicities was not shown due to the small sample size). Tumour factors (specific T and N stages) and whether the patient was diagnosed via emergency presentation route were from NCRAS. T and N stages were derived from pathological, imaging, and best staging information using a validated algorithm [19]. The presence of four major comorbidities which may directly affect the treatment decision, including heart failure, myocardial infarction, chronic pulmonary diseases, and diabetes with complications, was obtained from HES APC within six years and six months prior to cancer diagnosis [20].

Statistical Analysis

Descriptive analyses of all characteristics stratified by quintiles of socioeconomic deprivation were reported: continuous variables as median and interquartile range and categorical variables as number and proportion. We consider sociodemographic factors (i.e., age, sex, and ethnicity) and four major comorbidities as confounding factors and an interaction between age and deprivation. Tumour factors (specific T and N stages, and emergency presentation diagnostic route) were considered as potential mediators, as individuals from deprived areas might have a delayed diagnosis (presented as emergency or later stages)

which would limit treatment options and affect the timing of receiving treatments (e.g., emergency presentation might require urgent medical interventions). We included specific T and N stages as these are used in guidelines for treatment [6].

We conducted two sets of regression analyses to investigate the total and direct effect of deprivation on receiving NICE-recommended treatment [21]. Model 1 for the total effect included an interaction term between age and deprivation and adjusting for age, sex, ethnicity and four major comorbidities, where age was transformed by a restricted cubic spline with four knots placed at 5th, 35th, 65th, and 95th percentiles. Model 2 for the direct effect additionally adjusted for potential mediators including T and N stages, and emergency presentation, on top of model 1. We used multinominal logistic regression to model the main outcome – NICE-recommend treatment, an alternative treatment, and no treatment – and binary logistic regression to model secondary outcomes – surgery and adjuvant chemotherapy. We included Cancer Alliances as clusters in all models to estimate cluster robust standard errors for coefficients, as hospital trusts and other health and social care organisations within a Cancer Alliance share clinical and managerial leaders. After each regression model, the average marginal effect (causal effect) of deprivation (the most versus the least deprived) on outcomes at ages between 40 and 90 years were computed. In addition, we conducted causal mediation analysis [22] for each mediator – T and N stages, and emergency presentation – and secondary outcome using the "mediate" command in Stata.

We reported estimates with a 95% confidence interval (CI) and all statistical analyses were performed using Stata MP 18.0 (StataCorp, TX, US).

Results

Cohort Characteristics

Between 2012 and 2016, 21,928 individuals with stage III colon cancer met the eligibility criteria and 1560 (7.1%) were missing on deprivation, ethnicity, route to diagnosis, and T or N stages. Given the small amount of missing data, 20,368 individuals with complete-case data were included in the analyses. Missing data pattern is reported in Table S1 and characteristics of individuals included and excluded from the analyses are shown in Table S2, indicating similar distributions among the total sample and included individuals.

Table 1 shows the baseline characteristics of individuals included in the analysis by socioeconomic deprivation quintiles. The median age of diagnosis was 72.3 years (IQR: 63.8–79.7); there were more men than women (46.7%); around 95% were of White ethnicity. Distributions of age and sex were similar across quintiles. Compared to the least deprived quintile, the most deprived quintile had a higher proportion of non-White ethnicity [the most vs. the least deprived (same below): 8.6% vs. 2.9%], comorbidity (18.5% vs. 16.3%) and emergency presentation (19.0% vs. 13.1%). Patients from the most deprived areas tended to have a slightly higher proportion of advanced T (91.1% vs. 89.7%) and N stages (32.5% vs. 31.5%) than other groups but there were no clear socioeconomic trends.

Receipt of the NICE-Recommended Treatment

Table 2 shows the number of patients receiving the NICE-recommend treatment, and alternative treatment modality or no treatment by quintiles of the socioeconomic deprivation. Individuals from more deprived areas were more likely to receive no cancer-directed treatment – 9.4% of individuals from the most deprived vs. 5.5% of the least deprived – and less likely to receive the NICE-recommend treatment (47.5% vs. 55.3% in the most vs. least deprived).

Figure 1 shows the probability of receiving the NICE-recommend treatment, an alternative treatment or no treatment from the most and least deprived quintiles, estimated after multinomial logistic regression model 1 (total effect) and model 2 (direct effect). We observed socioeconomic inequalities in receipt of NICE-recommended treatment, evident by a statistical difference from 68 years old, and such inequalities continued until 85 years old but differed by age (Figure 1A). As expected, all individuals had a declining probability of receiving the NICE-recommend treatment as age increased, from almost 75% at 40 years to almost 0% at 90 years. However, individuals from the most deprived areas began to have a slow decline from the age of 50, whilst the least deprived quintile maintained a steady probability until the age of 60 years. The most deprived quintile also saw a rapid decline at a younger age, i.e., 60 years, compared to 70 years in the least deprived. For a 70-year-old individual, the probability of receiving NICE-recommended treatment was 70.8% (95% CI: 68.6, 73.1) for the least deprived quintile but 59.4% (53.7, 65.1) for the most deprived (Figure 1A; Table S3), leading to an absolute difference of 11.4%. Out of every nine 70-year-old individuals with stage III colon cancer, there would have been one more patient receiving the NICE-recommend treatment modalities (number needed to treat: 8.8), if we eliminated socioeconomic deprivation. Results from additional adjustments for potential mediators were almost identical (Figure 1B: direct effect), indicating that very little of these inequalities were mediated by T/N stages, or diagnosed via the emergency route (Table S3).

In contrast, the probability of receiving no treatment increased along with age. We found disparities in the probability of receiving no treatment from the age of 65 years, which substantially widened along with age, from almost 0% for a 40-year-old in both groups to 31.6% vs. 45.8% for a 90-year-old in the least vs. most deprived quintile. In addition, individuals over 85 years and from the least deprived areas tended to have a higher probability of getting an alternative treatment modality compared to those from the least deprived and vice versa in people aged under 85 years.

In short, socioeconomic inequalities in receipt of NICE-recommended treatment were observed at different ages: patients under the age of 65 years would normally receive

Table 1
Baseline characteristics by socioeconomic status quintiles in patients with stage III colon cancer in England between 2012-2016

	Total	1 (least deprived)	2	3	4	5 (most deprived)
	N=20,368	N=4049	N=5133	N=4433	N=3750	N=3003
Age at diagnosis, years						
Median (IQR)	72.3 (63.8–79.7)	72.6 (64.2–79.9)	72.7 (64.7–79.9)	72.4 (63.8–79.8)	71.6 (63.0–79.2)	71.3 (62.2–79.0)
18.0–49.9	1161 (5.7%)	194 (4.8%)	237 (4.6%)	275 (6.2%)	232 (6.2%)	223 (7.4%)
50.0–59.9	2250 (11.0%)	443 (10.9%)	509 (9.9%)	468 (10.6%)	462 (12.3%)	368 (12.3%)
60.0–69.9	5336 (26.2%)	1062 (26.2%)	1350 (26.3%)	1156 (26.1%)	978 (26.1%)	790 (26.3%)
70.0–79.9	6778 (33.3%)	1358 (33.5%)	1773 (34.5%)	1463 (33.0%)	1228 (32.7%)	956 (31.8%)
80.0–90.0	4843 (23.8%)	992 (24.5%)	1264 (24.6%)	1071 (24.2%)	850 (22.7%)	666 (22.2%)
Sex						
Men	10,855 (53.3%)	2141 (52.9%)	2740 (53.4%)	2357 (53.2%)	1995 (53.2%)	1622 (54.0%)
Women	9513 (46.7%)	1908 (47.1%)	2393 (46.6%)	2076 (46.8%)	1755 (46.8%)	1381 (46.0%)
Ethnicity						
White	19,261 (94.6%)	3933 (97.1%)	4970 (96.8%)	4147 (93.5%)	3465 (92.4%)	2746 (91.4%)
Non-White	1107 (5.4%)	116 (2.9%)	163 (3.2%)	286 (6.5%)	285 (7.6%)	257 (8.6%)
Diagnosed via Emergency presentation	2999 (14.7%)	529 (13.1%)	669 (13.0%)	639 (14.4%)	592 (15.8%)	570 (19.0%)
Heart failure	136 (0.7%)	30 (0.7%)	24 (0.5%)	30 (0.7%)	27 (0.7%)	25 (0.8%)
Myocardial infarction	176 (0.9%)	23 (0.6%)	39 (0.8%)	33 (0.7%)	40 (1.1%)	41 (1.4%)
Chronic pulmonary diseases	492 (2.4%)	74 (1.8%)	105 (2.0%)	101 (2.3%)	105 (2.8%)	107 (3.6%)
Diabetes with complications	40 (0.2%)	6 (0.1%)	8 (0.2%)	7 (0.2%)	13 (0.3%)	6 (0.2%)
T stage						
1-2	2107 (10.3%)	416 (10.3%)	534 (10.4%)	505 (11.4%)	384 (10.2%)	268 (8.9%)
3-4	18,261 (89.7%)	3633 (89.7%)	4599 (89.6%)	3928 (88.6%)	3366 (89.8%)	2735 (91.1%)
N stage						
1	13,885 (68.2%)	2774 (68.5%)	3496 (68.1%)	2996 (67.6%)	2593 (69.1%)	2026 (67.5%)
2	6483 (31.8%)	1275 (31.5%)	1637 (31.9%)	1437 (32.4%)	1157 (30.9%)	977 (32.5%)

IQR: Interquartile range.
*Four major comorbidities: relevant hospital admissions within six years and six months prior to the diagnosis of stage III colon cancer. Data are presented as number and percentage except age at diagnosis's Median and IQR.

Table 2
Treatment for patients with stage III colon cancer in England between 2012-2016 by socioeconomic status quintiles

	Total	1 (least deprived)	2	3	4	5 (most deprived)
	N=20,368	N=4049	N=5133	N=4433	N=3750	N=3003
Treatment overview						
No cancer-directed treatment	1305 (6.4%)	221 (5.5%)	276 (5.4%)	266 (6.0%)	261 (7.0%)	281 (9.4%)
Alternative treatment modality	8258 (40.5%)	1589 (39.2%)	2093 (40.8%)	1803 (40.7%)	1477 (39.4%)	1296 (43.2%)
NICE-recommended treatment (Surgery combined with adjuvant chemotherapy)	10,805 (53.0%)	2239 (55.3%)	2764 (53.8%)	2364 (53.3%)	2012 (53.7%)	1426 (47.5%)
Whether received surgery						
No	1686 (8.3%)	293 (7.2%)	367 (7.1%)	347 (7.8%)	334 (8.9%)	345 (11.5%)
Yes	18,682 (91.7%)	3756 (92.8%)	4766 (92.9%)	4086 (92.2%)	3416 (91.1%)	2658 (88.5%)
Patients who received surgery	N=18,682	N=3756	N=4766	N=4086	N=3416	N=2658
Surgery alone	7877 (42.2%)	1517 (40.4%)	2002 (42.0%)	1722 (42.1%)	1404 (41.1%)	1232 (46.4%)
Surgery with adjuvant chemotherapy	10,805 (57.8%)	2239 (59.6%)	2764 (58.0%)	2364 (57.9%)	2012 (58.9%)	1426 (53.6%)

NICE: The National Institute for Health and Care Excellence.

treatments, but individuals from the most deprived had a higher probability of receiving alternative treatment modalities while the least deprived tended to get NICE-recommended treatment; for ages between 65 and 85 years, inequalities persisted but the most deprived also started to have a higher probability of not getting any treatment; patients older than 85 years were unlikely to receive NICE-recommended treatment due to their age

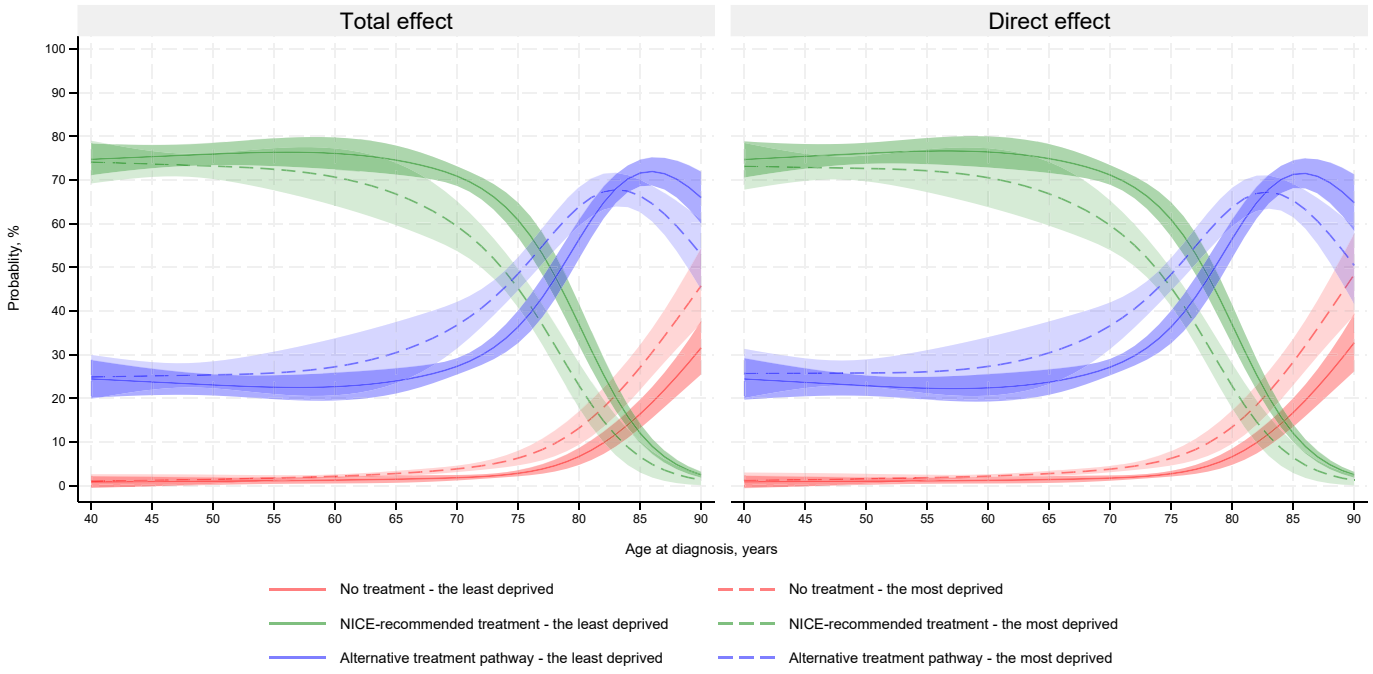

Fig 1. Probabilities of receiving NICE-recommended treatment, alternative treatment modality and no treatment in the least and most deprived patients with stage III colon cancer in England between 2012-2016.
Three colors represent three types of treatments patients received (green: NICE-recommended treatment; blue: Alternative treatment; red: no treatment); solid lines: the least deprived; dash lines: the most deprived. Areas indicate 95% confidence interval.
Model 1 (total effect) included an interaction between the spline-transformed age and deprivation quintiles, and adjusted for age, sex, ethnicity, heart failure, myocardial infarction, chronic pulmonary diseases, and diabetes with complications, and Model 2 (direct effect) additionally adjusted for T stage, N stage, and emergency presentation. The probabilities were predicted from multinomial logistic regressions as if all patients were in the most deprived quintile or in the least deprived quintile but keeping their other covariables, except the age, as observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(<5%), but still, the least deprived quintile had a higher probability of receiving alternative treatment modality and the gap in no treatment enlarged.

Similar patterns were observed when analysing income, education, and employment domains separately (Figure S2; Table S4).

Receipt of Specific Treatment Modality

To further explore the source of inequalities in NICE-recommend treatment, we investigated the receipt of surgery in the whole population and of adjuvant chemotherapy in individuals who received surgery. Table 2 shows that 88.5% vs. 92.8% of individuals from the most and least deprived areas received surgery, respectively; among them, 53.6% vs. 59.6% further received adjuvant chemotherapy, respectively. We then estimated the probability — average marginal effects after logistic regressions with adjustments for sociodemographic factors — of receiving surgery and adjuvant chemotherapy in the least and most deprived quintiles and corresponding odds ratios (ORs) (Figure 2; Table S5 and S6) by age.

We started to observe differences in the probabilities of receiving surgery from the age of 70 years, and inequalities widened until the age of 90 years (Figure 2A). For an 80-year-old, the probability was 91.5% (95% CI: 89.2, 93.8) in the least deprived and 83.9% (79.9, 88.0) in the most deprived (Figure 2A; Table S5). These results were also reflected in ORs (Figure 2C). Individuals from the most deprived areas had lower odds of receiving surgery than those from the least deprived, with a statistically significant OR from the age of 70 years. The strongest effect of socioeconomic deprivation was observed at around 80 years of age, with an OR of 0.48 (95% CI: 0.38, 0.62). The same trend was observed for income, employment, and education, however, the 95% CIs for the least and most deprived quintiles for education were overlapping at all ages (Figure S3).

In terms of adjuvant chemotherapy, we found that compared to those from the least deprived areas, the most deprived had an earlier (i.e., 60 vs. 65 years) decline in the probability of receiving adjuvant chemotherapy. Inequalities between the two groups in being administered adjuvant chemotherapy after the surgery were observed from 65 years to 85 years old; however, probabilities in both groups decreased towards null by the age of 90 years (Figure 2B). Patterns of probabilities for income, education and employment deprivation were similar to the combined socioeconomic deprivation analysis (Figure S3; Tables S5 and S6).

These results indicated that inequalities accumulated along the treatment pathway as socioeconomic inequalities in receipt of NICE-recommended treatment were led by both surgery and adjuvant chemotherapy.

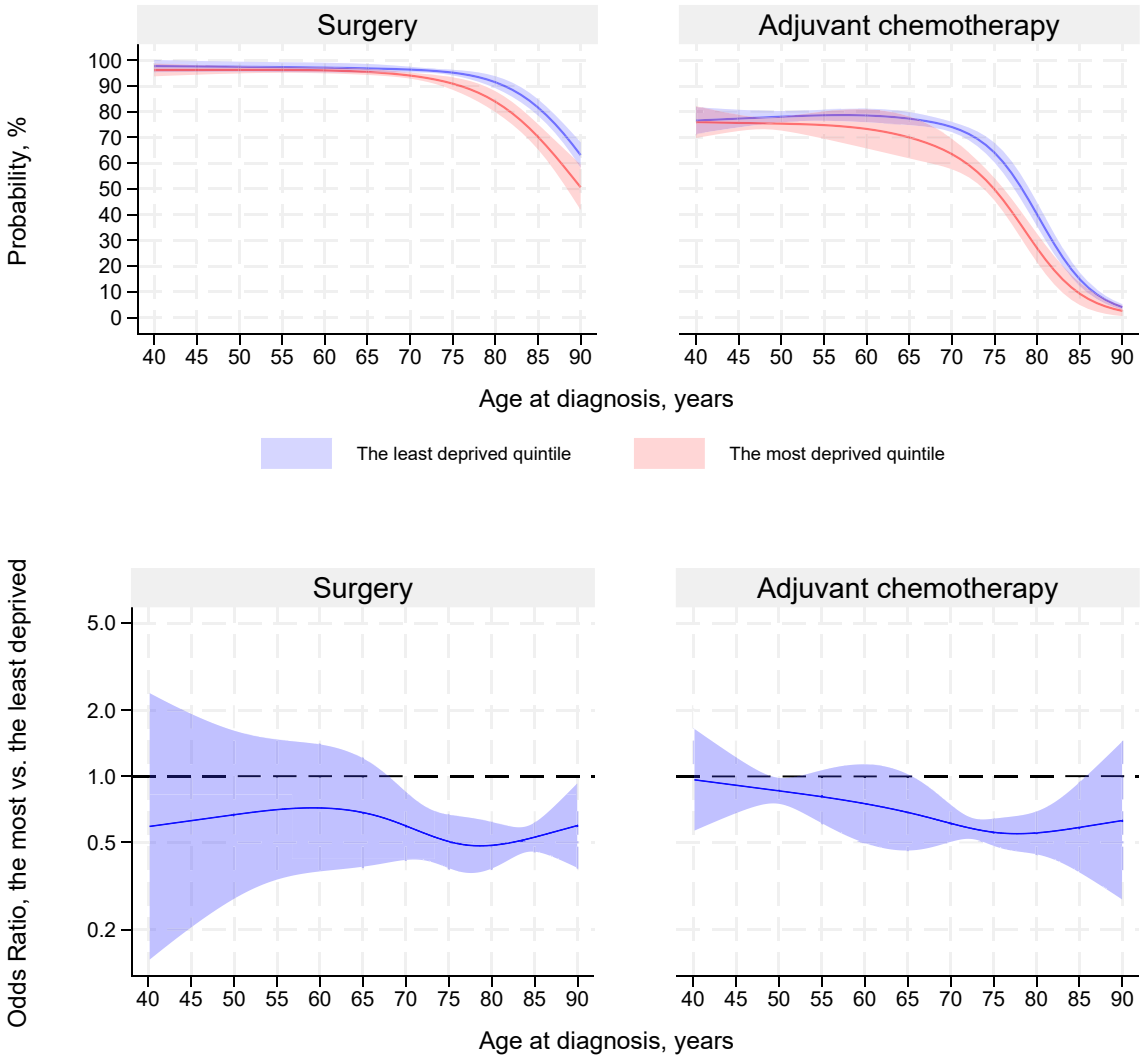

Fig 2. Probability receiving surgery and adjuvant chemotherapy by age in the most and least quintile of socioeconomic status and corresponding Odds Ratios in patients with stage III colon cancer in England between 2012-2016.
Top panel: Probability. Two colors represent the deprivation quintile (blue: the least deprived; red: the most deprived). Areas indicate 95% confidence interval.
Bottom panel: Odds Ratios (the most vs. the least quintile) of socioeconomic status. Blue areas indicate 95% confidence interval.
The probabilities were predicted after the logistic regression including an interaction between the spline-transformed age and deprivation quintiles, and adjusting for age, sex, ethnicity, heart failure, myocardial infarction, chronic pulmonary diseases, and diabetes with complications, as if all patients were in the most deprived quintile or in the least deprived quintile but keeping their other covariables, except the age, as observed.
Odds Ratios were derived from the same logistic regression.
The analysis of adjuvant chemotherapy only included those who received surgery (N = 18,682). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3 shows the total causal effect, proportion of indirect effect through mediators and direct effect of deprivation on surgery and adjuvant chemotherapy. Consistent with results for receipt of NICE-recommended treatment, limited mediation effects (<5%) for emergency presentation and T/N stage were observed for inequalities in the receipt of surgery or adjuvant chemotherapy.

It was estimated that up to 5000 patients would be diagnosed with stage III colon cancer every year in England. Out of every 1000 patients with colon cancer from the most deprived areas, compared with the least deprived, there would be 46 fewer patients receiving a major resection (95% CI: -59.4, -32.5), while for every 1000 patients who received surgery, there will be a further 88 fewer patients receiving adjuvant chemotherapy (95% CI: -110.2, -66.3).

Discussion

Using data from the English cancer registry between 2012 and 2016, this large population-based study indicated that socioeconomic inequalities in receipt of the NICE-

Table 3
Estimated risk differences per 1000 patients for the total causal effect and direct effect of socioeconomic status on surgery and adjuvant chemotherapy and proportions of effect through mediators

Outcome	Mediator	Risk difference per 1000 patients (95% confidence interval)[a]			Proportion of effect via mediator, %
		Total effect	Direct effect	Indirect effect (via mediator)	
Surgery	Emergency presentation	-46.0 (-59.4, -32.5)	-43.9 (-57.3, -30.5)	-2.3 (-4.4, -0.3)	5.1 (0.6, 9.5)
	T stage		-45.9 (-59.3, -32.4)	-0.1 (-0.6, 0.4)	0.2 (-0.8, 1.3)
	N stage		-46.0 (-59.4, -32.5)	0.0 (-0.1, 0.2)	-0.0 (-0.3, 0.3)
Adjuvant chemotherapy	Emergency presentation	-88.3 (-110.3, -66.3)	-84.9 (-107.0, -62.8)	-3.4 (-5.9, -0.9)	3.9 (0.9, 6.9)
	T stage		-89.8 (-111.8, -67.9)	1.6 (-0.4, 3.6)	-1.8 (-4.1, 0.5)
	N stage		-89.1 (-111.0, -67.2)	0.5 (-1.3, 2.2)	-0.5 (-2.5, 1.5)

[a] Patients from 1st quintile (the least deprived areas) are set as the reference group; a negative value of (total or direct) causal effect means compared to the reference group, patients from the most deprived areas had a lower "risk" of getting surgery or adjuvant chemotherapy.

recommend treatment in patients with stage III colon cancer still existed and differed by age, and tumour factors explained little of these. After adjusting for other sociodemographic factors and comorbidities, our data suggested that, for patients of the same age, those from deprived areas had inferior treatment modalities compared to those from less deprived areas, and such inequalities were observed at almost all ages. However, the widest inequalities were observed in patients aged between 65 and 85 years, and these were generated and accumulated at both surgery and adjuvant chemotherapy in the pathway. When both groups had a very low probability of receiving the NICE-recommend treatment (e.g., <5% in 85+ years), patients from the least deprived areas were still more likely to receive some alternative treatment modalities such as surgery, while those from the most deprived areas might receive no treatment at all. We observed similar patterns for income, education, employment, and our novel composite variable of deprivation combining the three. Our findings highlighted the persistent inequalities in treatment in individuals with stage III colon cancer, and policies are warranted to ensure equal access to treatment by socioeconomic status to reduce survival gaps.

Previous epidemiological studies have investigated age inequalities in access to a single treatment modality (i.e., surgery or adjuvant chemotherapy), and have shown that the probability of receiving treatment (surgery or chemotherapy) decreases along with age [3,7], this is consistent with our findings. For example, Hayes *et al.* reported that, although age-related inequalities in receipt of surgery and adjuvant chemotherapy narrowed over time in patients aged <80 years but did not diminish for the oldest patients [7]. Chronological age is not a criterion in determining the treatment, but age inequalities in treatment were constantly observed in real-world data. Apart from poorer health status, frailty and lower life expectancy in older patients (all rarely measured in real-world data), one possible explanation is that evidence contributing to current guidelines is mostly derived from RCTs, which have more restricted inclusion criteria, including age and comorbidities (more common in older people) [23], leading to uncertain effectiveness and safety of the treatment in older patients in clinical practice.

Socioeconomic inequalities in treatment for colon cancer were also reported in some previous studies, from access to treatment [24], time to treatment [25], and types of treatment [5]. Whether there is a causal relationship between socioeconomic status and access to treatment in universal healthcare settings is less certain, as many would argue that such an observation was masked by age or comorbidities, which have a greater impact on treatment decisions. In our study, however, we have investigated the interaction between age and socioeconomic deprivation and adjusted for four major comorbidities, and we further confirmed there were socioeconomic inequalities in receipt of the NICE-recommend treatment in patients with stage III colon cancer, and they varied by age. In addition, while most previous studies only measured a relative effect (e.g., ORs), we also presented absolute probabilities in the most and least deprived quintiles to better visualize the causal effect of socioeconomic deprivation. Moreover, we examined the treatment combination, as well as them separately, to depict different types of inequalities. For example, there were no socioeconomic disparities in receipt of the NICE-recommend treatment in individuals aged over 85 years. It should be noted that surgery or adjuvant chemotherapy does not come without any risk, and such associated risk (potential side effects that may reduce quality of life or even increase mortality) is higher in people at older age, which may also partly explain the overall low compliance to NICE-recommended treatment in this group. Still, patients from the least deprived areas were more likely to receive some alternative treatments, including surgery, while those from the most deprived areas were likely to receive none. This is an important finding that could help inform future research and ensure interventions to reduce inequalities are targeted at the most affected subgroups.

This study used a novel measure of socioeconomic deprivation containing the most individual-relevant domains: income, education and employment, rather than the overall IMD, which includes a domain related to health [26] that is highly correlated to the health outcome and other

environmental domains such as crime, and barriers to housing and living environment, or a single domain (e.g., income) as seen in other studies [3,4]. Our analyses have shown consistent results which proves the validity for its use. It should be noted that environmental/social factors would also indirectly affect the access to cancer treatment (e.g., availability of social support or treatment centres), and this novel measure only captures the individual aspect of deprivation, which captures the individual's ability to understand treatment options and navigate the complex healthcare system.

Factors contributing to these inequalities are likely complex, with physical, social and clinical attributes likely the key [27]. It is believed that increased comorbidities, delayed presentation and reduced health-seeking behaviours leading to a late diagnosis may limit treatments for patients [28], particularly for older patients. Indeed, data from this cohort showed that patients from the most deprived areas were more likely to have comorbidities, a higher proportion of diagnoses through emergency presentation and a lower proportion of diagnoses through screening. However, our results showed that these tumour factors explain little of these inequalities, consistent with an Australian study [29].

Whilst increased health-seeking behaviours in people with high income and educational attainment such as screening uptake [9,30] may lead to earlier diagnosis, we speculate that these individuals are more proactive in terms of navigating the healthcare system and communicating about their treatments making them more likely to get into the right hospital and treatment in the first place. A previous study has shown that colorectal patients were responsive to metrics for overall hospital quality and the availability of certain equipment (e.g., robotic surgery), but willingness (or ability) to cope with additional travel time may vary by deprivation [31], indicating policies allowing patient's choice may ultimately widen inequalities [32]. Travel distance and time to their treatment centre (i.e., access issue) was not measured in this study but it has also been suggested as one of the mechanisms [33]. Nevertheless, research is warranted to investigate this further. Furthermore, healthcare professionals' experiences, communication skills and patients' trust in them might also influence treatment decisions [34]. Future research should assess how the interplay between healthcare system factors, social and environmental aspects of deprivation, and individual factors contribute to these inequalities.

This study is the first UK-based study to investigate the socioeconomic inequalities in receipt of the NICE-recommend treatment along with mediation analysis, which allowed for a new understanding of inequalities in treatment for stage III colon cancer. In addition, this study utilized the national cancer registry data, and findings were generalisable to the whole of England. The linked NCRAS, SACT and HES databases were used to cross-validate the treatment records in our study. However, as with any routine data, misclassification or missing data can be an issue. We deem that the selection bias introduced by missing data is small as only less than 10% reported missing stage in all patients with colon cancer and 7% of patients with stage III had at least one missing value in our study. Additionally, the data sources did not contain information on patients who sought and obtained treatment outside the NHS (<1%) [16]. As individuals of higher socioeconomic status are more like to use private health services [35] and the COVID-19 pandemic affected NHS health services such as cancer diagnosis, surgeries, and anti-cancer therapies [36,37], this could mean that our findings could be an underestimate of the true current real-time values. We assumed that the ranking of an individual's LSOA reflects their true socioeconomic position, but this may introduce non-differential misclassification, and different ethnic groups may experience different relative deprivation within the same LSOA [38]. Therefore, data collection on individual socioeconomic status is warranted to support future research in this area. Moreover, as an observational study, we could not rule out residual confounding and further studies should investigate the mediating and confounding roles of system-wide factors to identify the most effective interventions. In addition, receipt of specific regimens merits further investigation as we only examined the presence of adjuvant chemotherapy in the current study, and some regimens may lead to a lower risk of side effects than others, which may increase the compliance and help reduce the inequalities. Finally, deaths that occurred during waiting time for treatment were not accounted for in this study, and it was difficult to measure access (offered) rather than receipt of treatment in real-world data. Therefore, inequalities in treatment measured in this study may also include inequalities in premature deaths reflecting severe cancer diagnosis and delayed cancer treatment, which is more common is elderly and deprived patients.

In summary, this study has provided further evidence of socioeconomic inequalities in receipt of NICE-recommended treatments for patients with stage III colon cancer, and this may explain the observed inequalities in survival. We have also disentangled the effect of age and found that those from the most socioeconomically deprived areas were less likely to receive the NICE-recommended treatment compared to their counterparts; instead, they tended to receive alternative or no treatment. Inequalities were observed at almost all ages but wider in patients aged 65–85 years, and tumour factors explained little of that, suggesting that other aspects, such as healthcare system-level factors, may contribute to these inequalities. Therefore, these age groups should be targeted by policymakers to help reduce socioeconomic inequalities. For example, it is crucial to work with patients to understand their care needs, allocate proportional resources to match their needs, and reduce barriers to access to maximize the use of services. On top of that, while individuals aged over 85 years from the least deprived areas could receive an alternative treatment such as surgery, those from the most deprived areas were more likely to receive no treatment at all. In addition, future research into socioeconomic inequalities could consider the use of the deprivation measure by combining income, education and employment domains as used in this study. In a system that should be free and fair

for all, it is imperative that the UK Government prioritize the levelling up of health to help reduce socioeconomic inequalities in receipt to cancer treatment that has now likely widened due to the COVID-19 pandemic.

Ethics Approval and Consent to Participate and Consent for Publication

The use of data has been approved by NHS Health Research Authority London – Central Research Ethics Committee (REC reference: 21/LO/0552; IRAS project ID: 279592) and this study protocol by LSHTM Ethics Online (reference: 27483).

Current legislation (GDPR and the DPA 2018) makes it permissible to use individual and even sensitive personal data, without consent, for bona fide non-interventional public health research, provided the relevant statutory and ethical permissions have been acquired from HRA and An NHS Research Ethics Committee, respectively. The wishes of patients who have withheld or withdrawn their consent are respected for identifiable data by the data providers (NHS and PHE). Data received by the ICON group have been anonymized.

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Author's Contributions

SL and BK designed the study, conducted data analysis, and drafted the article. BR acquired funding and data. All authors contributed to the interpretation of the data, critically revised the article and approved the final version. SL has full access to all the data and is responsible for the integrity of the work as a whole.

BK was a MSc student when the study was conducted. A part of this study was written up as a thesis to fulfil BK's Master degree in Epidemiology at The London School of Hygiene & Tropical Medicine.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

Data access is permitted via authorisation from NHS digital only. Clinical code lists and statistical codes are available at GitHub (https://github.com/supingling/colorectal_cancer).

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2025.103799.

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