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Inflammatory marker testing in primary care in the year before Hodgkin lymphoma diagnosis in patients aged 50 and under: A UK population-based case-control study

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Abstract

Background

Pro-inflammatory conditions are associated with increased risk of Hodgkin Lymphoma (HL), although the neoplastic process *per se* often induces an inflammatory response.

Aim

To examine pre-diagnostic inflammatory marker test use to identify changes that may define a 'diagnostic window' for potential earlier diagnosis.

Design and Setting

A matched case-control study set in UK primary care using Clinical Practice Research Datalink (CPRD) data (2002-2016).

Method

Primary care inflammatory marker test use and related findings were analysed in 839 HL patients and 5035 controls in the year pre-diagnosis. Poisson regression models were used to calculate monthly testing rates to examine changes over time in patterns of test use. Longitudinal trends in test results and the presence/absence of 'red-flag' symptoms were examined.

Results

71% of HL patients had an inflammatory marker test in the year pre-diagnosis versus 16% of controls (Odds Ratio 13.7, 95%CI 11.4-16.5, $p < 0.001$). The rate of inflammatory marker testing and mean levels of certain inflammatory marker results increased progressively during the year before HL diagnosis among cases while remaining stable in controls. Among HL patients with a pre-diagnostic test, two thirds (70%) had an abnormal result and among these, 43% had no other 'red-flag' presenting symptom/sign.

Conclusion

Increases in inflammatory marker requests and abnormal results occur in many HL patients several months pre-diagnosis, suggesting this period should be excluded in aetiological studies examining inflammation in HL development, and that a diagnostic time window of appreciable length exists in many HL patients, many of whom have no other red-flag features.

Key words

General practice, Hodgkin Lymphoma, inflammatory markers, diagnostic time window, blood tests

How this fits in (4 sentences)

Understanding the timing of the inflammatory response in HL may help identify opportunities for earlier diagnosis. In HL patients presenting to UK general practice, we observed greater than expected and increasing use of inflammatory marker tests in the year before diagnosis; Two thirds of inflammatory marker-tested HL patients had abnormal results, with almost half of patients in this group having no other recorded red-flag feature beyond their abnormal result. These findings provide proof of concept about the presence of a 'diagnostic window' during which HL diagnosis could have been expedited in at least some patients. Given the challenges of timely diagnosis in HL patients, inflammatory marker testing could help to expedite the diagnosis in those presenting with non-specific symptoms if supported and utilised by future advances in diagnostic technologies.

Introduction

The diagnosis of Hodgkin lymphoma (HL) in primary care is challenging and often delayed. This reflects its rarity, its predominance among young patients where cancer incidence is low and the fact that fewer than a third of patients present with 'red-flag' symptoms (unexplained lymphadenopathy or lumps) (1). Most HL patients present with non-specific symptoms, such as fatigue, abnormal sweating and pruritus, which have a broad range of differential diagnoses, including many benign conditions frequently encountered in patients consulting in primary care (2). New approaches to improving the diagnosis are therefore needed (3, 4).

Conditions associated with chronic inflammation represent risk factors for developing HL (4-10). Relatedly, raised inflammatory markers have been associated with increased risk of HL (11). However, the HL disease process itself could also be associated with an inflammatory response (12, 13); while this may introduce reverse causality ('protopathic') bias in aetiological studies examining the role of inflammation in HL risk, it could also represent an early marker of as-yet-undiagnosed HL, providing potential opportunities for more timely diagnosis.

The concept of a 'diagnostic time window' has been proposed to denote the pre-diagnostic period during which healthcare seeking and diagnostic activity increase from baseline. This represents the longest possible period during which the time-to-diagnosis could in principle be expedited in some patients (14-16). For aetiological studies, the length of the diagnostic window also defines the period during which reverse causality bias could occur when estimating causal associations; and the minimum pre-diagnostic period to be excluded from follow-up for this reason (16). Information about primary care blood test use has previously been used to estimate the length of such diagnostic windows for cancer sites other than HL (14, 17, 18). Raised inflammatory markers are predictive of HL risk (11), but when such abnormalities occur is unclear. Pottegård et al. suggest that a six-month lag-period should be applied in studies aiming to establish aetiological associations between exposure to a drug and risk of developing cancer to avoid reverse causality from increased prescribing in the lead up to cancer diagnosis (16). Examining associations between inflammatory markers and risk of developing HL is subject to similar concerns but the length of equivalent lag-periods to be applied is unknown.

Given the above background, we aimed to examine associations between primary care inflammatory marker blood test use/findings and subsequent HL diagnosis, and timing of changes in inflammatory markers pre-diagnosis.

Method

Data sources

We performed a matched case-control study using linked data from the UK Clinical Practice Research Datalink (CPRD) between 1st January 2002 – 31st July 2016. CPRD is a primary care electronic health record database containing anonymised information from GP consultations covering approximately 9% of all UK practices (in 2013) (19). Coded information on diagnoses, GP laboratory results and demographics are available. CPRD data were supplemented by linkage to Hospital Episode Statistic (HES) data (Set 13) for identification of HL diagnoses coded in ICD10 (International Classification of Diseases, 10th revision) for patients registered in England and Index of Multiple Deprivation (IMD) quintile to provide data on socioeconomic status.

Study population

HL has a bimodal age-specific incidence pattern with peaks in younger and older adults and likely different histological subtypes and aetiological processes in each group (9, 20). Individuals aged ≤ 50 years actively registered with a CPRD practice for more than a year with 'up-to-standard' data for research purposes during the study period were eligible for inclusion. This age group is where the majority of HL cases occur and where diagnostic difficulty is likely greater due to malignant disease being rare and less often considered in younger patients (21). Patients were excluded if they had a previous diagnosis of HL, or if the diagnosis was made within 1 year of registering with their practice (22). Cases were defined as a new diagnosis of HL in either CPRD or HES between 1st January 2003 – 31st July 2016 (Supplementary Table S1 for code lists), with the earliest recorded date of diagnosis taken as the index date. Six controls were individually matched to each case based on sex and age at index date (± 1 year of age) using concurrent matching (23). Each control was selected at random using a random number generator from the pool of eligible matches for each case. An index date was assigned to each control corresponding to the diagnosis date of their matched case. Data were analysed on all participants for 12 months prior to the index date.

Defining inflammatory marker blood tests

Six common inflammatory markers were selected: erythrocyte sedimentation rate (ESR), C reactive protein (CRP), plasma viscosity (PV), platelet count, ferritin concentration (whose

values all increase as part of the inflammatory response) and albumin (whose values decrease during the inflammatory response). All such tests during the 12 months pre-diagnosis/index date were included. Data were collected on test date, the total number of tests per patient during the 12-month period, and result (classified as normal or abnormal based on standard laboratory reference ranges). Where units of measurement varied, the most frequently used units and reference ranges were identified, and where possible values were converted accordingly, with biologically implausible values excluded. For repeat tests (of the same kind) on the same day only one was counted to prevent duplicates and the mean value of the results from that day was used.

Statistical analysis

Conditional logistic regression models were used to compare baseline characteristics of the study population and examine associations between both inflammatory marker test use ('any test vs none') and abnormal results (any vs none) with HL diagnosis in the following year, in cases and controls. When considering all inflammatory marker tests together, the number of test requests and number of abnormal results were treated as ordinal variables in the final model (i.e. 0,1, ≥ 2 requests per patient and 1, 2, ≥ 3 abnormal results across different tests in the year pre-diagnosis/index date). These paramaterisations improved model fit compared use of respective binary (yes/no) variables and were deemed more clinically informative as having two or more tests indicates potential follow-up testing and abnormal results across multiple different tests may increase likelihood of disease. The proportion of patients who received a test request from their GP was also calculated for sequential three-month time periods in the year before diagnosis/index date.

Mixed-effects Poisson regression analyses were used to examine time trends in GP inflammatory marker request rates. The total number of test requests per patient was modelled for each of the 12 months before HL diagnosis in cases and controls, including a random intercept for matching set given the matched study design. Testing rate ratios (RR) were used to compare monthly request rates in HL patients compared to a) their baseline rate, at 12 months pre-diagnosis and b) the corresponding rate in controls at synchronous time points to identify the month at which the RR becomes significantly greater for cases than for controls and estimate the maximum diagnostic window length. The above analyses were repeated separately for each of the six inflammatory marker tests.

Among HL cases only, we examined the timing of first inflammatory marker test events in the year before diagnosis, by comparing 'early' (defined as 3-12 months before diagnosis) to 'late' (<3 months before diagnosis) tests, and estimating the proportion with an 'early' abnormal result versus exclusively 'late' abnormal results. Further, as a supplementary analysis patient information on the presence of consultations with recorded 'red-flag' symptoms for HL in the year preceding diagnosis (lymphadenopathy/lumps, night sweats and weight loss (24) – supplementary table S2 for code lists) was also examined. This was used to explore how often inflammatory marker tests and abnormal findings occurred in HL patients without 'red-flag' symptoms to estimate the proportion of HL patients in which abnormal findings could be particularly useful. This was done by cross tabulating red-flag symptom status (yes/no) by a) inflammatory marker test use status, b) *abnormal* inflammatory test status, and c) 'early' *abnormal* inflammatory test status. Analyses were performed using Stata (version 16; StataCorp, College Station, TX, USA).

Results

839 cases of HL were matched to 5035 controls (Supplementary Figure S1). 47% of cases were identified using CPRD alone, 9% were identified using HES alone and 44% were identified in both datasets. In addition to age and sex (matching variables), cases and controls also had comparable socioeconomic status (supplementary table S3). In the year before diagnosis 71% of HL patients had at least one of the six examined inflammatory marker tests (CRP, ESR, PV, platelets, ferritin or albumin) compared to 16% of controls ($P < 0.001$) and tested patients had 14-fold greater odds of HL diagnosis compared to controls (Odds Ratio (OR) 13.7, 95%CI 11.4-16.5, $p < 0.001$). The odds of HL diagnosis increased with increasing number of tests ($p < 0.001$, Table 1). Similar increases were observed when considering each inflammatory marker test individually (Table 1). Among the 594 HL patients who had a test in the year pre-diagnosis, 42% had an 'early' test (requested ≥ 3 months before diagnosis) and 1 in 5 had an 'early' abnormal result (Supplementary tables S4).

Among tested patients, inflammatory markers were also more often abnormal in the year preceding diagnosis or index date in HL patients (70%) compared to controls (18%) ($p < 0.001$, Table 1). Greater number of abnormal test results in the year pre-diagnosis (across different types of inflammatory markers) was also associated with greater odds of HL ($p < 0.001$, Table 1).

Proportion of patients tested over time

The proportion of patients having at least one inflammatory marker test was consistently higher in HL patients than controls for each sequential 3-month time period in the year pre-diagnosis, with similar patterns across all six tests (Figure 1). The most notable increase in test use among HL patients was seen for platelet count (part of full blood count) and albumin concentration (part of liver function tests), the proportion of HL patients having these tests gradually increasing from <10% at 10-12 months pre-diagnosis to 56% and 43% in the 3 months immediately preceding diagnosis, respectively, while remaining stable <10% in controls (Figure 1).

Test request rates over time

Among HL patients, the rate of inflammatory marker requests increased throughout the year pre-diagnosis, with monthly testing rates increasing 13-fold from 66 tests per 1000 patients at baseline to 836 tests per 1000 patients in the month immediately before diagnosis (RR 12.8, 95%CI 9.7-16.8, $P < 0.001$), while remaining stable in controls over the same period (Figure 2, Supplementary table S5).

Considering the use of different inflammatory marker tests individually over time, among HL patients, an increase in GP tests request rates was apparent for each of the six inflammatory marker tests throughout the year pre-diagnosis (Figure 3).

Inflammatory marker test results over time

Among tested patients, trends over time in inflammatory markers levels of the four most commonly requested inflammatory markers with large enough number of observations showed that mean monthly values of ESR and platelet levels were consistently higher in HL patients for all 12 months pre-diagnosis and from 11 months pre-diagnosis for CRP. Mean albumin levels were consistently lower than controls for all 12 months pre-diagnosis (Figure 4). While remaining stable in controls, among HL patients, mean CRP levels increased throughout the year before diagnosis, mean ESR levels from 11 months pre-diagnosis and mean platelet levels from around 7 months pre-diagnosis.

Co-occurrence of inflammatory marker test use with red-flag symptoms

Among all inflammatory marker-tested HL patients, 39% (234/594) had no 'red-flag' symptoms recorded in the year before diagnosis (Table 2). Of the 413 inflammatory marker-tested HL patients with an abnormal result 43% (176/413) had no red-flag symptoms recorded (supplementary table S6).

Similarly, among all tested HL patients without red-flag symptoms, 75% (176/234) had at least one abnormal result and 25% (59/234) had an 'early' abnormal result.

Discussion

Summary

In Hodgkin Lymphoma patients, both GP requests for inflammatory marker blood tests and inflammatory marker levels increase throughout the year before diagnosis when compared to controls. Studies investigating aetiological associations between markers of inflammation and HL should exclude the year pre-diagnosis to avoid reverse causation. These increases also represent early signals of disease and indicate that a 'diagnostic time window' of appreciable length exists for earlier diagnosis of HL in at least some patients.

Over 70% of all HL patients had at least one inflammatory marker blood test in the year before diagnosis, with two thirds of these patients having at least one abnormal result and 1 in 5 having an 'early' abnormal result 3 months or longer before their diagnosis. Close to half of all HL patients with an abnormal result had no other 'red-flag' features recorded. Inflammatory marker tests may therefore provide information that could support earlier diagnosis in large proportions of HL patients presenting with non-specific symptoms to primary care, if enabled by advances in diagnostic processes and technologies.

Strengths and Limitations

This UK nationwide study is, to the best of our knowledge, the first to explore patterns of inflammatory marker tests in primary care over time before a diagnosis of HL, together with consideration of whether abnormal results occurred in patients presenting with or without 'red-flag' symptoms. Strengths include the large sample size, which is representative of the UK population (19), and its primary care setting; these aspects increase the generalisability of the findings. Test request rates were plotted alongside monthly RRs to determine diagnostic time window length. The recording of lymphoma cases in CPRD concords highly with English population-based cancer registration data (25), and was further enhanced by linkage to hospital records (26). Because blood results are electronically incorporated into patients' primary care records the likelihood of inaccuracies is reduced. However, in a relatively small proportion of

patients, blood tests may have been requested by their GP but not completed and therefore not coded. In some patients a 'red-flag' symptom may have been present but not coded, resulting in possible underestimation of 'red-flag' feature frequency, however given the clinical importance of these symptoms and high awareness among GPs such under-coding is likely rare (27). Our study included HL patients ≤ 50 years. Because HL subtypes and their association with inflammation are likely to differ by age (8, 9, 28-34), findings are not necessarily generalisable to the diagnostic pathway of older HL patients. We could not assess for overdispersion, therefore, if present the confidence intervals we present may be somewhat narrower than they should be. We used a 12-month pre-diagnosis period in our study, guided by prior epidemiological studies indicating that the length of this period is adequate to assess reverse causality from medication prescriptions and cancer incidence (16). However, we were not able to confirm if this also applies for the association between inflammatory markers and HL. Future, larger, studies should examine longer pre-diagnostic periods and additional blood tests to see if similar patterns are seen.

Comparison with existing literature

A few studies have investigated the association between primary care inflammatory marker tests and subsequent cancer diagnosis. These have shown that raised platelets (35, 36), ESR, CRP and PV (37, 38) and hypoalbuminaemia (39) are risk markers for undiagnosed cancer of any site within the next year, particularly in patients with persistent and/or greater inflammatory marker abnormalities, or ≥ 2 abnormal inflammatory marker test results (37, 38). Raised inflammatory markers (platelets, ESR, CRP or PV) are associated with increased risk of subsequent HL diagnosis in patients aged ≥ 40 years with red-flag symptoms (11). Studies of other cancer sites reported raised CRP levels to be predictive of lung cancer up to 12 months before diagnosis (18); and increases in ESR and PV levels up to 2 years before a myeloma diagnosis (17).

Our study adds to these findings by demonstrating for the first time that similar phenomena exist for HL, profiling additional inflammatory marker blood tests, demonstrating the value of abnormal inflammatory results in patients without 'red-flag' symptoms, and by determining the length of the lag-period that should be applied to future aetiological studies examining inflammation and HL development.

Implications for research and practice

Increases in inflammatory marker levels in HL patients were concentrated in the months leading up to diagnosis which strongly suggests that they are a result of the evolving neoplastic process (12) rather than related to pre-existing chronic inflammatory conditions. Therefore, a minimum of 12-months pre-diagnosis should be excluded in studies examining aetiological associations between inflammatory markers and HL risk to ensure associations do not reflect underlying malignancy.

The increased rate of inflammatory marker requests during the year before HL diagnosis suggests many HL patients are presenting to their GP several months pre-diagnosis with symptoms prompting further investigation and the presence of an appreciable 'diagnostic time window' for potential earlier diagnosis in some HL patients if this increased activity can be detected.

HL patients frequently have abnormal results several months pre-diagnosis, often in the absence of red-flag symptoms like lymphadenopathy. This indicates that an inflammatory response is also occurring in HL patients with non-specific symptoms and abnormal inflammatory marker levels can represent early detectable signs of HL in this group. As such abnormalities are relatively common in primary care and HL is a rare disease, the predictive value for HL of any such single result in isolation will likely be low. However, if supported by advances in diagnostic processes and technologies, there is potential for evidence from blood test results to be combined with other pre-diagnostic features to provide information that could support earlier HL diagnosis in some patients.

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Ethical Approval:

The protocol for this project was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number:16_237). Generic ethical approval for observational studies conducted using anonymised CPRD data with approval from ISAC has been granted from a National Research Ethics Service Committee (NRES). The study was performed in accordance with the Declaration of Helsinki

Competing Interests:

The authors declare no potential conflicts of interest.

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Tables and Figures:

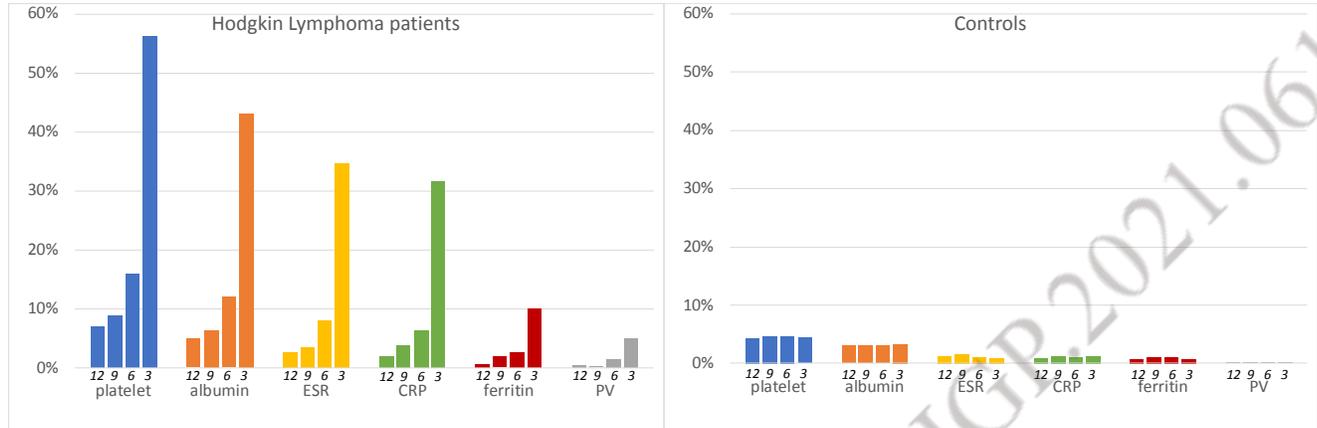
Table 1: Association between Hodgkin lymphoma and inflammatory marker blood tests in the year preceding diagnosis/index date. HL, Hodgkin's Lymphoma; *percentage out of all patients who had the test; †12 months pre-diagnosis date in cases or 12 months pre-index date in controls; SD, standard deviation; m, months; P value from Likelihood-ratio test from regression models (separate for each test) where case status was the outcome and each inflammatory marker test related variable was the exposure or from t-test for comparison of means

Blood test	Characteristics	Cases of HL (n=839)	Controls (n=5035)	Absolute difference	Odds Ratio (95%CI)	P value
Any inflammatory marker test	Tested in last year*	594 (70.8%)	816 (16.2%)	55%	13.7 (11.4 – 16.5)	<0.001
	Number of tests					
	1	43 (5.1%)	167 (3.3%)	1.8%	4.66 (3.21 – 6.75)	<0.001
	≥2	551 (65.7%)	649 (12.9%)	52.8%	16.49 (13.57 – 20.04)	
	Median (range, IQR)	3 (0-33, 5)	0 (0-24, 0)	3	-	-
Number of different test types with an abnormal result	1*	167 (28.1%)	119 (14.6%)	13.5%	15.7 (11.7 – 21.1)	<0.001
	2*	135 (22.7%)	24 (2.9%)	19.8%	80.7 (45.0 – 145.0)	
	≥3*	111 (18.7%)	3 (0.4%)	18.3%	484.0 (146.7-1596.5)	
Platelet	Tested in last year*	578 (68.9%)	742 (14.7%)	54.2%	14.1 (11.7 – 17.0)	<0.001
	Had abnormal result*	198 (34.3%)	59 (8.0%)	26.3%	8.07 (5.02 – 12.99)	<0.001
	Mean value (SD)	354.2 10 ⁹ /L (143.2)	267.6 10 ⁹ /L (74.8)	86.6 10 ⁹ /L	-	<0.001
Albumin	Tested in last year*	452 (53.9%)	542 (10.8%)	43.1%	11.1 (9.2 – 13.3)	<0.001
	Had abnormal result*	95 (21.0%)	36 (6.6%)	14.4%	3.16 (1.79 – 5.59)	<0.001
	Mean value (SD)	39.8g/L (6.0)	43.3g/L (4.5)	-3.5g/L	-	<0.001
ESR	Tested in last year*	361 (43.0%)	213 (4.2%)	38.8%	17.7 (14.2 – 22.1)	<0.001
	Had abnormal result*	266 (73.7%)	78 (36.6%)	37.1%	6.37 (2.85 – 14.27)	<0.001
	Mean value (SD)	39.0mm/h (32.0)	11.4mm/h (13.0)	27.6mm/h	-	<0.001
CRP	Tested in last year*	320 (38.1%)	191 (3.8%)	34.3%	17.8 (14.1 – 22.4)	<0.001
	Had abnormal result*	217 (67.8%)	32 (16.8%)	51.0%	50.0 (6.9 – 364.2)	<0.001
	Mean value (SD)	49.9mg/L (57.7)	7.9mg/L (16.9)	42.0mg/L	-	<0.001
PV	Tested in last year*	51 (6.1%)	28 (0.6%)	5.5%	11.0 (6.9 – 17.4)	<0.001
	Had abnormal result*	39 (76.5%)	10 (35.7%)	40.8%	-	-
	Mean value (SD)	1.9mPa.s (0.2)	1.7 mPa.s (0.1)	0.2mPa.s	-	<0.001
Ferritin	Tested in last year*	113 (13.5%)	160 (3.2%)	10.3%	4.97 (3.82 – 6.45)	<0.001
	Had abnormal result (high)*	30 (26.5%)	5 (3.1%)	23.4%	3.00 (0.31 – 28.84)	0.34
	Mean value (SD)	230.5ug/L (296.4)	64.9 ug/L (95.4)	165.6ug/L	-	<0.001

Table 2: The frequency of red-flag symptoms in Hodgkin lymphoma patients who had inflammatory marker tests (n=594) *Lump is defined as in the head/neck, axillary, groin or not otherwise specified

	Platelet (578)	Albumin (452)	ESR (361)	CRP (320)	Ferritin (113)	PV (51)
Number of patients tested						
No red-flag symptoms	226 (39.1%)	187 (41.4%)	142 (39.3%)	137 (42.8%)	64 (56.6%)	16 (31.4%)
Lymphadenopathy	167 (28.9%)	118 (26.1%)	99 (27.4%)	81 (25.3%)	24 (21.2%)	18 (35.3%)
Lump*	211 (36.5%)	155 (34.3%)	128 (35.5%)	111 (34.7%)	23 (20.4%)	27 (52.9%)
Night Sweats	26 (4.5%)	23 (5.1%)	19 (5.3%)	20 (6.3%)	6 (5.3%)	1 (2.0%)
Weight Loss	25 (4.3%)	21 (4.7%)	16 (4.4%)	15 (4.7%)	5 (4.4%)	4 (7.8%)

Figure 1: Proportion of patients with a GP requests for inflammatory marker blood test: For sequential 3-month periods in the year prior to diagnosis/index date in Hodgkin's Lymphoma patients and controls. Numbers underneath bars represent months prior to diagnosis/index date.



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Figure 2: GP requests for any inflammatory marker blood test in Hodgkin's Lymphoma patients and controls. Upper part: Rate of blood test requests (test requests per 1000 patients per month) 12 months prior to diagnosis/index date with 95% CIs. Lower part: The Rate Ratio for test requests compared to baseline at -12 months with 95% CIs.

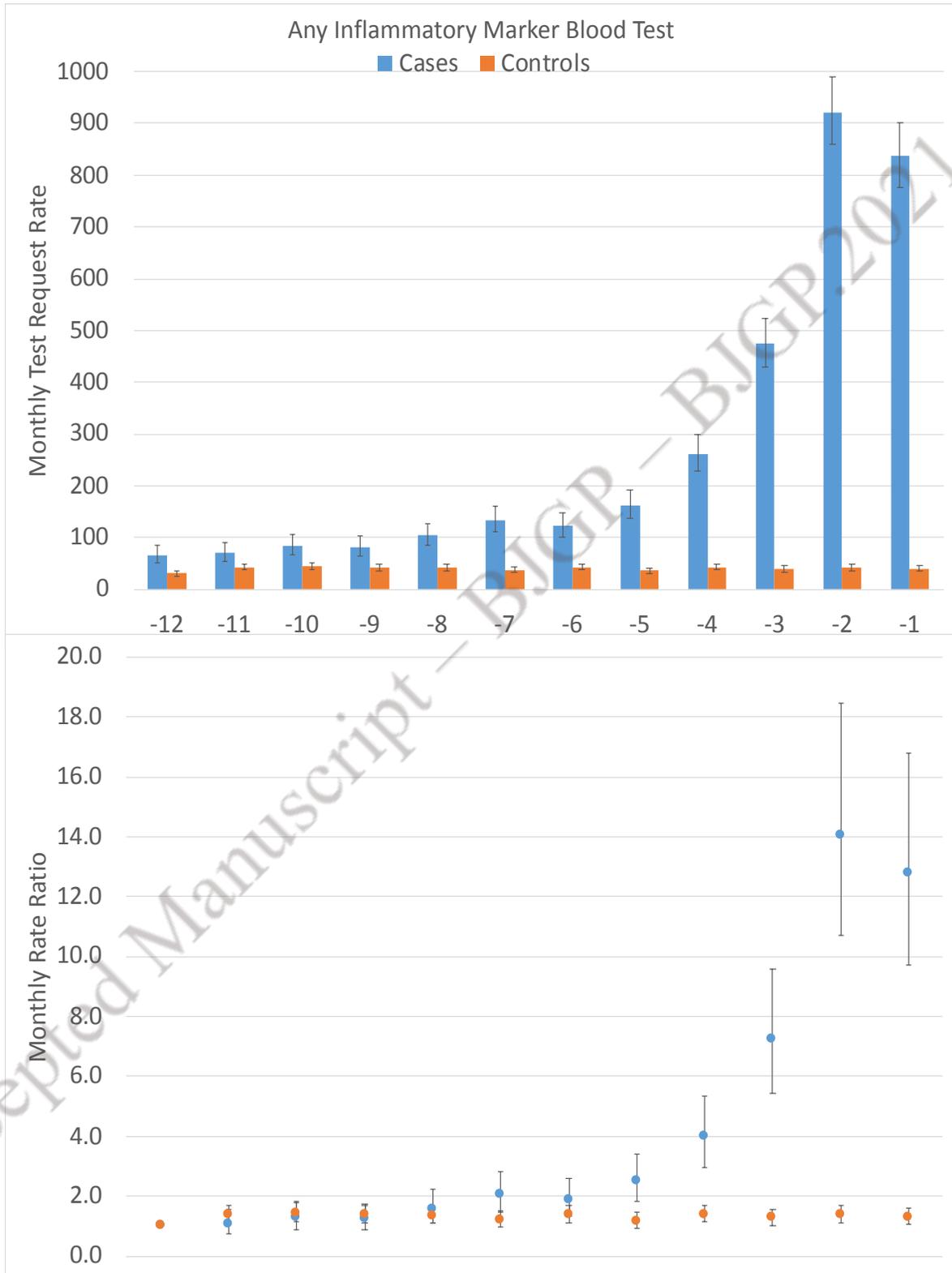
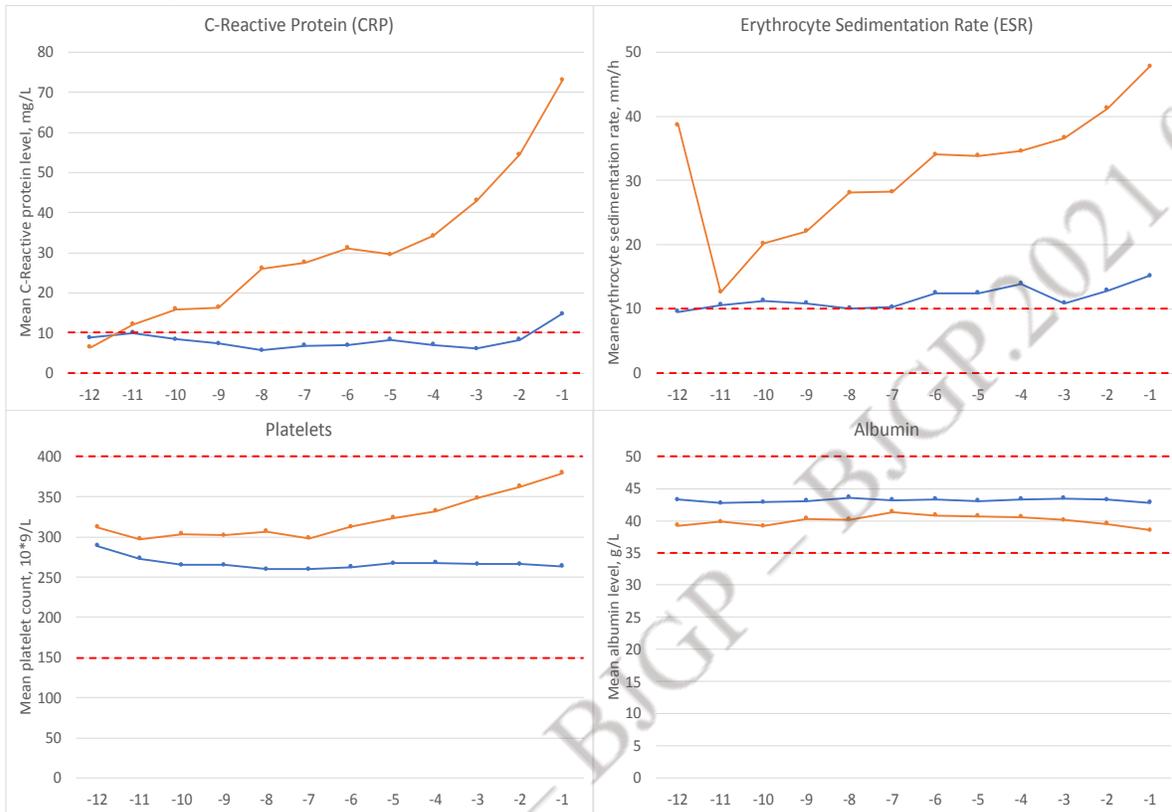


Figure 3: GP requests for inflammatory marker blood test in Hodgkin's Lymphoma patients and controls by test type. Upper part: Rates of blood test requests (test requests per 1000 patients per month) 12 months prior to diagnosis/index date. Lower part: The Rate Ratio for test requests compared to baseline at -12 months with 95% CIs.



Figure 4: Inflammatory marker blood test trajectories 12 months before diagnosis for the four most commonly requested tests - mean test value per month using a 3 month moving average in General Practice for tested Hodgkin lymphoma patients (orange line) and controls (blue line). Dashed line represents upper and lower limit of normal range.



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