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**Running head:**

Mortality among patients with polymyalgia rheumatica

**Title:**

Mortality among patients with polymyalgia rheumatica: A retrospective cohort study

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**ABSTRACT**

**Objective:** To determine whether a diagnosis of polymyalgia rheumatica (PMR) is associated with premature mortality.

**Methods:** We extracted anonymised electronic medical records of patients over the age of 40 years, who were eligible for linkage with the Office for National Statistics (ONS) Death Registration dataset, from the Clinical Practice Research Datalink from 1990-2016. Patients with PMR were individually matched by age, sex and registered General Practice with up to 5 controls without PMR. The total number and proportion of deaths and mortality rates were calculated. The mortality rate ratio (MRR), with 95% confidence interval (CI), adjusted for age, sex, region, smoking status, body mass index (BMI), and alcohol consumption, was calculated using Poisson regression. The twenty most common causes of death were tabulated.

**Results:** 18,943 patients with PMR were matched to 87,801 controls. Mean (standard deviation) follow-up after date of diagnosis was 8.0 (4.4) years in patients with PMR, and 7.9 (4.6) in controls. PMR was not associated with an increase in the risk of death (adjusted MRR 1.00 [95% CI 0.97, 1.03]) compared to matched controls. Causes of death were broadly similar between patients with PMR and controls, although patients with PMR were slightly more likely to have a vascular cause of death recorded (24% vs 23%).

**Conclusions:** A diagnosis with PMR does not appear to increase the risk of premature death. Minor variations in cause of death were observed, but overall this study is reassuring for patients with PMR and clinicians.

## SIGNIFICANCE AND INNOVATIONS

1. This is the largest ever study of mortality among patient with polymyalgia rheumatica, including over 100,000 patients and controls
2. Polymyalgia rheumatica does not increase the risk of premature death
3. The cause of death is similar among patients with polymyalgia rheumatica compared to controls

## INTRODUCTION

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition that predominantly affects older people, (1) and can have a devastating impact on patients' lives. Classical symptoms of PMR include stiffness, pain and impairment to daily activities. (2) A recent study of PMR epidemiology estimated the incidence and prevalence of PMR to be 95.9 [94.9, 96.8] per 100,000 person years and 0.85% respectively. (1)

A recent systematic review found that patients with PMR had a higher burden of comorbid disease when compared to age and sex matched controls. (3) However, three previous studies reported no difference or reduced premature mortality among patients diagnosed with PMR. (4–6)

Given the high burden of comorbid disease among patients with PMR, the raised systemic levels of inflammation associated with it, and the prolonged glucocorticoid (GC) therapy with which many patients with PMR are treated, it is important to ascertain whether a diagnosis of PMR is associated with an increased risk of premature mortality.

## PATIENTS AND METHODS

### Data source

The National Health Service (NHS) provides healthcare to all UK residents, and 98% of people in the UK are registered with a General Practice. Around 90% of patient contacts in the UK occur in primary care. (7) We utilised data from the Clinical Practice Research Datalink (CPRD; version July 2017), which contains data from 17 million contributing patients across 718 (7.5% of the total) practices. This database, containing electronic, coded information collected during the course of routine healthcare, is representative of the UK population in terms of age, sex and ethnicity (8) and has been used extensively for research. The CPRD's Independent Scientific Advisory Committee (ISAC) approved this study, (protocol number: 17_203RA).

The CPRD can be linked to death registration data from the Office for National Statistics (ONS). Only practices based in England are eligible for linkage and, of those, 75% have consented. (8) Where consent exists, patient level data is linked via NHS Digital to the other established data sources.

The linkage between CPRD and death registration data is available from January 1998 until February 2018. This dataset also contains information on the official date of death, the date of registration of death, the underlying cause of death and any other contributing factors given. (9)

### Definition of incident PMR

The exposed group were aged 40 years and over with a CPRD recorded PMR diagnosis. Each patient had a Read code diagnosis of PMR (N20 Polymyalgia rheumatica; N200.00 Giant cell arteritis with polymyalgia rheumatica) between 02/01/1998 and 01/01/2018 and two prescriptions of GCs, the first made within six months of PMR diagnosis, and the second within six months of

the first. This replicates previous CPRD PMR studies (10) and provides supporting information as to the accuracy of the diagnosis. In addition to these requirements, each had at least three years of continuous follow up prior to date of diagnosis with PMR (the index date).

**Selection of unexposed group**

Each individual with PMR was matched with up to five unexposed people. The matching criteria employed were: 1) year of birth +/- 3 years, 2) sex and 3) registered practice. The index date for each exposed person was assigned to their matched unexposed group, who were also required to have been contributing data on that date and for 3 years prior.

**Study period**

The start of this study was defined as the index date, which was the date of PMR diagnosis for the exposed and their matched group. Follow up continued until the earliest of these events: 1) 1st January 2018 (the end of the period encompassed by ONS Death Registration data), 2) the date when a patient transferred out of the practice, 3) the last date of data collection from the practice, or 4) the date of death.

**Statistical analysis**

Descriptive statistics were used to find average age of the exposed and unexposed as well as the proportion of exposed and unexposed per region, sex, smoking status, BMI category, alcohol consumption status, as well as follow up prior to, and following, index date. This was to ensure that the exposed and unexposed were similar.

The primary outcome measures were total number of deaths in exposed and unexposed groups, as well as estimated mortality rate per 1,000 person years (with 95% confidence intervals [CI]). Estimates of survival were constructed using Kaplan-Meier methods. ONS Death Registration data includes the date of death, the date of death registration and cause of death. For this study the date of death was used and the cause of death was included as a secondary analysis.

A Poisson regression model was used to calculate the mortality rate ratio (MRR) with 95% CI in order to compare the mortality rate of patients with PMR to those without. This figure was adjusted for age, sex, region, smoking status, BMI, and alcohol consumption. If data regarding covariates were missing, patients were assumed to be non-smokers, consume no alcohol and have a normal BMI.

## RESULTS

A total of 18,943 patients with PMR and 87,801 matched unexposed individuals were included in the analysis. The demographic information of patients is presented in table 1. The average age at diagnosis, sex and region of GP practice were very similar between the exposed and unexposed. The mean age of the exposed was greater than the unexposed by 0.3 years, and the mean (standard deviation) follow up period was 7.9 (4.6) years. The three disease risk modifiers, BMI, smoking and alcohol consumption, were similar between the exposed and unexposed, however data were less likely to be missing in the exposed compared to unexposed.

The total number, and proportion, of patients with and without PMR who died, as well as the mortality rate ratio and twenty most common causes of death, are shown in table 2. Figure 1 describes the Kaplan Meier estimate of mortality in the first ten years after diagnosis in patients with and without PMR. Over the whole time period, a slightly higher proportion of patients with PMR died compared to patients without PMR (31.9% and 31.0%). However, the mortality rates

were similar, at 39.9 and 39.2 per 1,000 patient years and the mortality rate ratio of 1.00 (0.97, 1.03), which was adjusted for age, sex, region, smoking status, BMI, and alcohol consumption, showed there was no difference between the two groups. A sensitivity analysis where patients with co-existent GCA were excluded from the sample found the same results.

## DISCUSSION

### Main findings

This study confirms that a diagnosis of PMR does not have a significant impact on life expectancy. The causes of death in patients with PMR were broadly similar to those of matched controls; however a slightly higher proportion of patients with PMR died due to vascular causes and a slightly lower proportion died due to neoplastic conditions.

### Strengths and limitations

This is the largest study to estimate the effect that a diagnosis of PMR has upon life expectancy. The sample used a large, established database of patients who are representative of the UK population, (11) and is drawn from primary care, where the majority of patients with PMR are managed. (12) The Office for National Statistics (ONS) is the UK's recognised national statistical institute. All deaths in the UK must be registered and are therefore recorded in this dataset. This data source is used to report trends in mortality and guide national healthcare policy. Therefore, the ONS dataset is the most complete source of this information.

A potential limitation is the initial ascertainment of PMR. In CPRD it is not possible to authenticate diagnoses by ensuring each patient fulfils validated classification criteria for PMR. No diagnostic criteria nor specific diagnostic test exists for PMR, therefore even if access to

individual patients were possible, confirmation of diagnosis can never be fully achieved. However, ensuring that all patients have at least two GC prescriptions in their records provides more confidence in the diagnosis of PMR. This method has been used before in previously published studies in CPRD of PMR. (13) Furthermore, this study can provide reassurance for patients with a diagnosis with PMR that no association with premature mortality was found.

The cause of death may be incorrectly coded. Some studies have estimated for example that cardiovascular causes of death may be overstated in mortality data. (14) However, a study from the ONS found that only 12% of the broad underlying causes of death needed to be amended following medical examiner scrutiny. (15) Furthermore, there is no reason to suppose that the presence of PMR would lead to a difference in error rate compared to those without.

Another potential bias is surveillance bias, wherein people who are diagnosed with PMR may be more likely to be followed up more closely in primary care. This would mean that comorbidities may be diagnosed sooner and treated more effectively in these patients, which could lead to improvement in survival, mitigating any potential reduction in survival caused by the disease itself.

Previous studies have found that patients with PMR have a high comorbidity burden, with a possible increased risk of vascular disease. (3,16) In this study, a greater proportion of patients with PMR had a vascular cause of death recorded. Conversely, a smaller proportion of patients with PMR were recorded as dying due to cancer. Therefore, the neutral effect of PMR on mortality observed in the current study may be caused by the increase in the risk of vascular disease in this patient group balancing the reduction in the risk of death due to cancer among patients with PMR.

**Comparison to other studies**

Two previous studies based in Norway have reported reduced mortality rates in patients with PMR and attributed this to improved medical surveillance among patients with PMR. (4,5) One study from the United States however found no significant difference in mortality in patients with PMR when compared to the general population, (6) while another more recent study with more than 40 years of data also concluded that survival among patients with PMR was no worse compared to the general population. (17) In this study, no significant difference in mortality, between patients

with PMR compared to matched controls, was found, with an adjusted mortality rate ratio of 1.00 [0.97, 1.03]. This study is therefore reassuring for those who receive a diagnosis of PMR.

**Conclusion and clinical implications**

This study is the first to estimate the effect that PMR has on mortality in a large sample of patients using primary care and linked data. Overall, the mortality rate in patients with PMR, when compared to matched controls, is not significantly different, although there are some minor variations in the recorded cause of death.

Our previous work has demonstrated that patients with PMR were less likely than controls to have a previous diagnosis of cancer or neurological diseases. Therefore, it could be speculated that patients with PMR group should actually have improved survival when compared to matched controls. The neutral effect observed may be due to increased rates of vascular disease in patients with PMR balancing the reduction in risk of death due to cancer.

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Table 1: Demographic information of included patients

| | Total | Exposed | Unexposed |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) | 73.6 (8.9) | 73.8 (9.1) | 73.5 (8.9) |
| **Sex (%)** | | | |
| Male | 34,559 (32.4) | 6,273 (33.1) | 28,286 (32.2) |
| Female | 72,185 (67.6) | 12,670 (66.9) | 59,515 (67.8) |
| **Region (%)** | | | |
| North East | 1,740 (1.6) | 306 (1.6) | 1,434 (1.6) |
| North West | 13,428 (12.6) | 2,366 (12.5) | 11,062 (12.6) |
| Yorkshire & the Humber | 3,574 (3.4) | 639 (3.4) | 2,935 (3.3) |
| East Midlands | 2,853 (2.7) | 499 (2.6) | 2,354 (2.7) |
| West Midlands | 15,032 (14.1) | 2,609 (13.8) | 12,423 (14.1) |
| East of England | 15,320 (14.4) | 2,674 (14.1) | 12,646 (14.4) |
| South West | 17,137 (16.1) | 3,042 (16.1) | 14,095 (16.1) |
| South Central | 14,075 (13.2) | 2,517 (13.3) | 11,558 (13.2) |
| London | 7,732 (7.2) | 1,456 (7.7) | 6,276 (7.1) |
| South East Coast | 15,853 (14.9) | 2,835 (15.0) | 13,018 (14.8) |
| **BMI category** | | | |
| Normal(18.5-24.9) | 34,552 (32.4) | 6,052 (31.9) | 28,500 (32.5) |
| Underweight (<18.5) | 1,986 (1.9) | 0,221 (1.2) | 1,765 (2) |
| Overweight (25-29.9) | 36,515 (34.2) | 6,923 (36.5) | 29,592 (33.7) |
| Obese (>=30) | 21,521 (20.2) | 4,132 (21.8) | 17,389 (19.8) |
| Missing | 12,170 (11.4) | 1,615 (8.5) | 10,555 (12) |
| **Smoking** | | | |
| Non-smoker | 90,111 (84.4) | 16,582 (87.5) | 73,529 (83.8) |
| Smoker | 11,823 (11.1) | 1,827 (9.6) | 9,996 (11.4) |
| Missing | 4,810 (4.5) | 0,534 (2.8) | 4,276 (4.9) |
| **Alcohol** | | | |
| Never / no current | 21,546 (20.2) | 3,779 (19.9) | 17,767 (20.2) |
| <10 units per week | 55,927 (52.4) | 10,369 (54.7) | 45,558 (51.9) |

| | Total | Exposed | Unexposed |
|---|---|---|---|
| 10 or more units per week | 16,133 (15.1) | 2,942 (15.5) | 13,191 (15) |
| Missing | 13,138 (12.3) | 1,853 (9.8) | 11,285 (12.9) |
| **Follow up (years)** | | | |
| Mean (SD) | 7.9 (4.6) | 8.0 (4.4) | 7.9 (4.6) |

Table 2: Number, proportion and cause of death (in order of frequency) in patients with and without PMR

| | **Exposed** | **N (%)** | **Unexposed** | **N (%)** |
|---|---|---|---|---|
| Total number of deaths | | 6,046 (31.9) | Total number of deaths | 27,224 (31.0) |
| Rate per 1,000 patient years (95% CI) | | 39.9 (38.9, 41) | Rate per 1,000 patient years (95% CI) | 39.2 (38.7, 40) |
| Mortality rate ratio (95% CI) | | | 1.00 (0.97, 1.03) | |
| **Causes of death** | | | | |
| 1 | Chronic ischaemic heart disease | 464 (7.7) | Chronic ischaemic heart disease | 1,810 (6.7) |
| 2 | Acute myocardial infarction | 409 (6.8) | Chronic obstructive pulmonary disease | 1,652 (6.1) |
| 3 | Chronic obstructive | 327 (5.4) | Acute myocardial | 1,651 (6.1) |

| | Exposed | N (%) | Unexposed | N (%) |
|---|---|---|---|---|
| | pulmonary disease | | infarction | |
| 4 | Malignant neoplasm: Bronchus or lung | 316 (5.2) | Malignant neoplasm: Bronchus or lung | 1,631 (6.0) |
| 5 | Bronchopneumonia | 258 (4.3) | Bronchopneumonia | 989 (3.6) |
| 6 | Pneumonia | 243 (4.0) | Atherosclerotic heart disease | 967 (3.6) |
| 7 | Atherosclerotic heart disease | 187 (3.1) | Pneumonia | 889 (3.3) |
| 8 | Vascular dementia | 123 (2.0) | Alzheimer disease | 790 (2.9) |
| 9 | Urinary tract infection | 115 (1.9) | Malignant neoplasm: Breast | 709 (2.6) |
| 10 | Malignant neoplasm: Pancreas | 109 (1.8) | Vascular dementia | 604 (2.2) |
| 11 | Cerebrovascular disease | 108 (1.8) | Cerebrovascular disease | 585 (2.2) |
| 12 | Alzheimer disease | 106 (1.8) | Malignant neoplasm without specification | 460 (1.7) |
| 13 | Malignant neoplasm without specification. | 103 (1.7) | Malignant neoplasm: Pancreas | 447 (1.6) |
| 14 | Malignant neoplasm: Breast | 99 (1.6) | Urinary tract infection | 416 (1.5) |
| 15 | Other interstitial pulmonary diseases | 93 (1.5) | Malignant neoplasm: Colon | 410 (1.5) |
| 16 | Congestive heart failure | 84 (1.4) | Malignant neoplasm: Oesophagus | 371 (1.4) |
| 17 | Malignant neoplasm: Colon | 84 (1.4) | Malignant neoplasm: Bladder | 312 (1.2) |
| 18 | Aortic (valve) stenosis | 71 (1.2) | Congestive heart failure | 309 (1.1) |
| 19 | Cerebral infarction | 68 (1.1) | Intracerebral haemorrhage | 302 (1.1) |

| Exposed | | N (%) | Unexposed | N (%) |
|---|---|---|---|---|
| 20 | Malignant neoplasm: oesophagus | 67 (1.1) | Other respiratory disorders | 291 (1.1) |
| | Others | 2,612 (43.8) | Others | 11,629 (41.6) |

Figure 1: Kaplan-Meier survival plot of patients with and without PMR