An evaluation of the association between C-reactive protein, the change in C-reactive protein over one year, and all-cause mortality in chronic immune-mediated inflammatory disease managed in UK general practice

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Objectives. To evaluate the association between systemic inflammation, as measured by CRP, and all-cause mortality. To also evaluate the association between change in CRP status (sub-acute, ≤10 mg/l and acute >10 mg/l) and all-cause mortality.

Methods. A cohort of patients was selected from The Health Improvement Network (THIN) data set of anonymized patient-level data from UK general practice. Patients were selected if they had a diagnosis of RA, psoriasis, AS or PsA. Survival was evaluated using Cox proportional hazards regression models (CPHMs).

Results. A total of 11,362 cases had at least one CRP measurement. Analysis grouped by each additional unit increase in log-CRP (range 1–6) across the observed range was associated with a 21% increase in the hazard ratio (HR) of death, after controlling for cardiovascular risk factors (P < 0.001). This observation was consistent in separate analysis of cases with either RA or psoriasis. Repeated CRP observations around 1 yr apart were recorded in 2802 subjects. After controlling for confounding factors, in cases whose CRP changed from sub-acute (≤10 mg/l) to acute (>10 mg/l), the HR for death increased 2-fold (P < 0.001) relative to cases whose CRP remained sub-acute. In comparison, among those subjects whose CRP was reduced from acute to sub-acute, the HR was virtually identical to those who stayed sub-acute (P = 0.571).

Conclusions. CRP level predicted all-cause mortality after standardization for traditional risk factors, as did change in CRP status from sub-acute to acute observed over 1 yr.

Key words: C-reactive protein, Systemic inflammation, Survival, Rheumatoid arthritis, Psoriasis, Ankylosing spondylitis, Psoriatic arthritis.

Introduction

Elevated CRP has been found to be associated with increased risk of cardiovascular disease [1, 2]. Evidence is emerging for the pro-atherogenic role of CRP [1, 3]. This has considerable clinical significance since vascular inflammation is modifiable. There are considerable experimental data linking CRP to endothelial dysfunction, vascular remodelling and key stages of the atherothrombotic process. Exogenous CRP also activates both inflammation and coagulation when administered to healthy volunteers [4], an effect independent of endotoxin or other contaminants [3].

Resolution of this hypothesis is of particular interest in the management of autoimmune conditions where chronic elevation of CRP accelerates atherosclerosis [5], and thereby potentially increases mortality. Cardiovascular diseases and their risk factors are more common in patients with RA, PsA and AS than in matched controls [6]. Although CRP has been shown to be a poor predictor of RA incidence [7], it is central in the evaluation of disease progression and response to therapeutic intervention [8–10] and increasingly suspected as a pro-atherogenic agent in affected patients [11–13]. Similar associations are evident in psoriasis (Pso) [14] where the relative risk of myocardial infarction in young severe patients is elevated 3-fold over disease-free controls after adjustment for relevant baseline cardiovascular risk factors [15]. PsA patients exhibit greater intima–media wall thickness of the common carotid artery than healthy controls who independently correlate with parameters of disease activity and conventional risk factors of atherosclerosis [16]. Endothelial function has been shown to be impaired in AS [17] and men with AS have perturbances in several coronary heart disease (CHD) risk factors, which appear to be driven principally by systemic inflammatory mediators [18].

Despite the large body of epidemiological data relating to CRP, few studies have examined the relationship between longitudinal change in CRP and prognosis [19]. In a recent study of routine laboratory data collected in hospital practice [20], cases whose CRP changed over a 1 yr period from normal (≤3 mg/l) to an elevated status (>3 mg/l) experienced a 6.7-fold increase in the hazard ratio (HR) for all-cause mortality compared with those whose CRP remained normal. In contrast, among those whose CRP returned to normal the risk of death was halved compared with those among whom CRP remained persistently elevated over a 1-yr observation. However, in patients with immune-mediated chronic inflammatory disease, the link between CRP and mortality does not appear to have been studied explicitly despite evidence of excess mortality in these conditions [21–24].

In this study, we aimed to evaluate the association between CRP and all-cause mortality as well as the change in CRP status and all-cause mortality among patients with chronic inflammatory disease using routine data from UK general practice.

Patients and methods

Data analysed in this study were derived from routine general practice in the UK. Ethical approval was provided by the Cambridge MREC. These data were sourced from a proprietary health data resource, The Health Improvement Network (THIN) [25], akin to the General Practice Research Database (GPRD) [26], a widely recognized source of UK general practice (GP) data. THIN data are collected in a non-interventional way from the daily record keeping of primary care physicians in the United Kingdom. The records are anonymized at the collection stage so that researchers have access to an encrypted identifier for the physician’s office and the patient. They provide a longitudinal medical record for each patient. Currently, the data set consists of contributions from over 300 practices and data from ~5 million people.
patients of whom over 2.3 million are actively registered with the practices and can be prospectively followed. The remaining patients have historical data but have either left the practice or died. There are nearly 30 million patient-years of computerized data in THIN. Patients have full data for 6 yrs, on average, and some may have up to 15 yrs’ observations. Data from THIN consist of four categories that detail the following: (i) subject demographic details; (ii) medical history (diagnoses); (iii) test results and additional health-related data, such as smoking status; and (iv) drug treatments. The current data cover a period of observation from 1997 to 2007.

Clinical classification
Data were extracted for patients with a diagnosis for at least one of the four diagnoses for an immune-mediated chronic inflammatory disorder: Pso; RA; AS, and PA. Since these indications are chronic conditions, a selection diagnosis was only assigned if the subject had >1 diagnostic code on two different dates. A marker for ‘newly diagnosed’ was assigned if the patient had at least 6 months case history prior to first rheumatic diagnostic code. All-cause mortality was taken from the date of death recorded by THIN. Cause of death is not systematically recorded thereby necessitating use of all-cause mortality rather than disease-specific mortality, e.g. cardiovascular.

Laboratory data
The key biochemical marker in this investigation, serum CRP concentration, is reported as provided in THIN. It was not possible to determine whether the assays were of high sensitivity; therefore, it was decided to categorize individuals’ CRP level according to the scientific statement recently issued by the American Heart Association and Centers for Disease Control and Prevention [27], a method used previously in large epidemiological studies [28]. A sub-acute level of CRP was defined as \( \leq 10 \text{mg/l} \) whilst levels in excess of \( 10 \text{mg/l} \) were defined as representing an acute inflammatory process. CRP observations were utilized only if they had a >0 in order to be sure if this was a true observation and not a null value attributed 0 (zero) systematically or at data entry. In total, there were 77 590 CRP observations from 11 362 cases. Recorded total cholesterol (TC) observations were similarly treated.

Case selection
Cases with at least one CRP observation were selected if they had not had a diagnosis of an acute ischaemic event (acute myocardial infarction or stroke) recorded within 30 days before and after the first CRP observation. Similarly, the follow-up CRP level was defined as the mean of values occurring within a further 90 days of the second (1 yr) observation. CRP change was then defined for the period as sub-acute→sub-acute (SS), sub-acute→acute (SA), acute→sub-acute (A→S) and acute→acute (AA). Classification by the method previously used in the hospital study [20] was not feasible in this instance as too few cases in the CRP change subgroup met the American Heart Association (AHA) criteria for ‘normal’ CRP (\( \leq 3 \text{mg/l} \)). Any case in the CRP change subgroup that had a recorded diagnosis of an acute ischaemic event during their CRP observation period (\( \pm 30 \text{ days} \)) was excluded from analysis.

Statistical methods
Survival was evaluated using a Cox proportional hazards regression model (CPHM), using SPSS® v15, SPSS, Chicago, IL, USA. Independent covariates of survival were tested using a manual forward inclusion method with a threshold significance of \( P=0.05 \) as the criterion for inclusion in the final models. Time to event was measured from the date of the last-reported CRP observation. Surviving cases were right-censored by their last known contact date.

Results
The initial data capture contained 46 232 cases, 97% of whom had a single diagnosis of either Pso, RA, AS or PA. The majority of these cases had either Pso (70.6%) or RA (24.2%). A significant proportion of the original cohort (63%) was labelled as new diagnoses with diagnostic proportions identical to the overall group.

First CRP measurement
Twenty-five per cent of the initial cohort, some 11 362 cases, had at least one CRP measurement, though the proportion attributable to each of the four diseases changed substantially in favour of RA (50.9%), followed by Pso. The mean age at first CRP measurement was 56.4 yrs and 36.3% were males; though significant differences emerged between the disease groups (Table 1), males were less represented among those with RA (28.3%) and older on average. Within the total cohort there were 860 deaths (7.6%) of any cause within the follow-up period. CPHM showed that each unit increase in log-CRP was associated with a 21% increase in the HR (95% CI 11%, 33%) (Table 2) after controlling for age, gender, BMI, smoking status and number of visits to the GP in the year prior to CRP measurement. Repeated separate adjusted survival analysis for RA cases and Pso cases showed this relationship to be remarkably consistent [HR 1.20 (95% CI 1.07, 1.34; \( P=0.002 \)] and HR 1.24 (95% CI 1.05, 1.47; \( P=0.012 \), respectively) despite reduced numbers and differing event rates.

CRP change
Repeated CRP observations at 1 yr were available for 2806 subjects. Among these, the majority (53.6%) had a first quarter
average CRP in the acute range (>10 mg/l). Acute CRP cases were somewhat older than sub-acute cases (60.6 yrs vs 58.3 yrs; \( P < 0.001 \)) and had more men (36.0% vs 29.2%; \( P < 0.001 \); Table 3). Neither mean total cholesterol (TC) nor mean BMI showed any statistically significant difference between CRP categories. The likelihood of death within 3 yrs of the CRP observation period also showed a significant increase across the CRP categories (\( P < 0.001 \)), more than trebling between those who remained sub-acute and acute during the 1-yr CRP observation period (sub-acute, 3.4%; acute, 10.7%; \( P < 0.001 \)). The likelihood of death among cases whose CRP rose during observation was approximately twice that of cases whose CRP fell (9.2% vs 4.9%; \( P < 0.001 \)).

In a CPHM model of all-cause mortality controlling for age, smoking status and number of prior GP visits, the likelihood of death was markedly different between CRP change category (Table 4 and Fig. 1). Compared with stable sub-acute (SS) cases, the hazard of death among increasers (SA) and persistently acute (AA) cases approximately doubled (\( P = 0.008 \) and \( P < 0.001 \), respectively). The HR for those returning to a sub-acute state (A→S) showed no statistically significant difference from the SS reference cases (\( P = 0.571 \)).

**Discussion**

It was found in these data from UK general practice that an increasing level of sub-acute CRP was associated with an increased risk of mortality for patients with chronic inflammatory diagnoses. Further, the likelihood of death was markedly greater in those whose CRP had increased from sub-acute to acutely elevated levels than those whose CRP decreased over a 1-yr observation period. The magnitude of the HRs compared with other covariates suggested that CRP change was an important marker of mortality, in addition to and independently of previous CRP status.

Regarding the impact of change in CRP status over time, people whose CRP increased to being acutely high over the yearly...
Association between CRP and all-cause mortality

TABLE 4. CPHM for all-cause mortality after 1 yr CRP observation (n = 2563, 6.8% deaths)

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<th>Variables in the equation</th>
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<th>s.e.</th>
<th>Sig.</th>
<th>HR</th>
<th>95% CI for HR</th>
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<td>Lower</td>
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<td>Male gender (cf. female)</td>
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<td>Age at index CRP, yr</td>
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<td>Number of GP visits year prior to CRP</td>
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<td>CRP change (cf. sub-acute→sub-acute)</td>
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Excluded covariates: prior ischaemic disease.

Fig. 1. Survival plot for all-cause mortality by CRP change category standardized for age, sex, smoking status and number of GP visits in the year prior to first CRP.

Period has similar but slightly lower risk than those whose CRP remained acutely high. Importantly, those subjects whose CRP declined to a sub-acute level were observed to have reduced risk, and of the same magnitude as those with low initial CRP readings. These findings are entirely consistent with two recent studies [20, 31].

The availability of other vascular risk factors such as blood pressure measurements, obesity, serum cholesterol and smoking status has enabled the significance of CRP status and the changing CRP status to be thoroughly evaluated. Missing data for lipid profiles in the CRP change sub-group analysis precluded its inclusion in these survival analyses but as total serum cholesterol did not reach threshold significance in the snapshot CRP analysis, there was no specific reason to think it may have exerted undue influence in the subgroup analysis, especially given the low variation between the CRP change groups. The highly sensitive CRP assay currently in widespread use may enable more accurate detection of lower CRP levels but was not available here in sufficient numbers to allow meaningful analysis of this parameter. This, we believe, did not affect the capacity of these data to investigate the principal research question [32].

The analysis of cardiovascular event prognosis was not possible in this data set since too few events emerged to power an analysis with a detectable HR [33, 34]. Analysis of disease-specific mortality would have been desirable for testing the initial hypotheses but was not possible with the available data. As the THIN data set is not linked to the Office for National Statistics and relies on practice recording of death, some deaths are likely to have been missed from this analysis. The extent to which this introduces bias to the findings cannot be assessed but we believe it to be small.

Surprisingly, annual follow-up CRP measurements were available for only 6% of the cases initially selected for analysis. There would seem to be a compelling case for routine interval measurement of CRP in this group of patients. A study of interval measurement of CRP in general practice would form a useful line of further research.

Importantly, retrospective data such as the source used here are not suitable for the investigation of cause and effect; only association. This would require an interventional study. However, the finding that increasing levels of CRP over time lends credence to the hypothesis that there is a causal relationship. There is a theoretical possibility that these findings are only generalizable to those subjects who had their CRP measured in these data, with potential confounding by therapeutic intervention. However, the consistent association, in both direction and magnitude, found between CRP and survival in separate adjusted analyses for RA and PsO cases reduces the likelihood of this confounding.

Despite their limitations, these findings do illustrate the striking association between CRP change observed over 1 yr and subsequent all-cause mortality. Among those in whom CRP reduced from an acute to sub-acute status, the risk of death returned to the same level as those whose CRP remained sub-acute over the observation period. In the context of the weight of evidence supporting the role of CRP as promoter of disease and not simply a marker, these findings will be of interest to clinicians in assessing disease prognosis in RA and PsO and therapeutic strategies that will reduce CRP most effectively.

Conclusion

Increasing levels of acute inflammation, as measured by CRP, was found to be associated with an increasing risk of all-cause mortality. Furthermore, this risk was increased in subjects whose CRP was found to increase over time.

Rheumatology key messages

- Higher CRP is independently associated with significantly increased risk of death.
- Reduction in inflammatory status correlates independently with reduced risk of death.

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References

1 Sciriha BM, Morrow DA. Is C-reactive protein an innocent bystander or proathero-
genic culprit? The verdict is still out. Circulation 2006;113:2128–34.


Poole CD, Conway P, Currie CJ. An evaluation of the association between the first observation and the longitudinal change in C-reactive protein, and all-cause mortality. Heart 2008;94:457–62.


