





Serum C-reactive protein is associated with earlier mortality across different interstitial lung diseases

Carmel J. W. Stock^{1,2}  | William G. Bray^{1,2} | Vasilis Kouranos^{1,2} | Joseph Jacob^{3,4} | Maria Kokosi^{1,2} | Peter M. George^{1,2} | Felix Chua^{1,2}  | Athol U. Wells^{1,2}  | Piersante Sestini⁵ | Elisabetta A. Renzoni^{1,2} 

¹Interstitial Lung Disease Unit, Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation Trust, London, UK

²Margaret Turner Warwick Centre for Fibrosing Lung Disease, National Heart and Lung Institute, Imperial College London, London, UK

³Satsuma Lab, Centre for Medical Image Computing, Department of Computer Science, UCL, London, UK

⁴UCL Respiratory, UCL, London, UK

⁵Respiratory Diseases, University of Siena, Siena, Italy

Correspondence

Carmel J. W. Stock
Email: c.stock@rbht.nhs.uk

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Abstract

Background and Objective: The acute-phase protein C-reactive protein (CRP) is known to be associated with poor outcomes in cancer and cardiovascular disease, but there is limited evidence of its prognostic implications in interstitial lung diseases (ILDs). We therefore set out to test whether baseline serum CRP levels are associated with mortality in four different ILDs.

Methods: In this retrospective study, clinically measured CRP levels, as well as baseline demographics and lung function measures, were collected for ILD patients first presenting to the Royal Brompton Hospital between January 2010 and December 2019. Cox regression analysis was used to determine the relationship with 5-year mortality.

Results: Patients included in the study were: idiopathic pulmonary fibrosis (IPF) $n = 422$, fibrotic hypersensitivity pneumonitis (fHP) $n = 233$, rheumatoid arthritis associated ILD (RA-ILD) $n = 111$ and Systemic Sclerosis associated ILD (SSc-ILD) $n = 86$. Patients with a recent history of infection were excluded. Higher CRP levels were associated with shorter 5-year survival in all four disease groups on both univariable analyses, and after adjusting for age, gender, smoking history, immunosuppressive therapy and baseline disease severity (IPF: HR (95% CI): 1.3 (1.1–1.5), $p = 0.003$, fHP: 1.5 (1.2–1.9), $p = 0.001$, RA-ILD: 1.4 (1.1–1.84), $p = 0.01$ and SSc-ILD: 2.7 (1.6–4.5), $p < 0.001$).

Conclusion: Higher CRP levels are independently associated with reduced 5-year survival in IPF, fHP, RA-ILD and SSc-ILD.

KEYWORDS

C-reactive protein, CRP, fHP, fibrotic hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, ILD, interstitial lung disease, IPF, RA-ILD, rheumatoid arthritis associated ILD, SSc-ILD, systemic sclerosis associated ILD

INTRODUCTION

The contribution of inflammation to the pathogenesis of many interstitial lung diseases (ILDs) is well recognized. C-reactive protein (CRP) is an acute-phase protein utilized as a non-specific marker of infection and inflammation, widely used in routine clinical practice. However, only a few

studies have investigated the impact of CRP levels on survival in ILD, with inconclusive findings. Higher CRP levels were associated with a worse 5-year survival in 57 idiopathic pulmonary fibrosis (IPF) patients, even after adjustment for smoking, lung function and presence of fibroblastic foci on biopsy.¹ In 150 patients with connective tissue disease-associated ILD, higher CRP levels were associated with increased mortality, although unclear whether survival analysis was adjusted for baseline ILD severity.²

Piersante Sestini and Elisabetta A. Renzoni contributed equally to this study.

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In a small study of patients with rheumatoid arthritis associated ILD (RA-ILD), although CRP levels were higher in those who died during follow-up ($n = 28$) compared with those who did not ($n = 49$), the association with survival was not significant on logistic regression analysis.³ In a study of 266 early systemic sclerosis (SSc) patients, regardless of ILD status, baseline CRP levels correlated with higher mortality, independent of age, sex, ethnicity, BMI and treatment, although baseline lung function was not accounted for.⁴ In a study of 19 SSc-ILD patients treated with cyclophosphamide, higher CRP levels, as well as less ground glass opacities on HRCT, were predictive of significant ILD progression after adjusting for use of other therapies. Higher CRP was an independent predictor of mortality in 375 patients with SSc,⁵ and CRP levels were higher in SSc patients with ILD than those without ILD.⁶

We set out to investigate the association between clinically measured baseline CRP levels and mortality in four ILD subgroups; IPF, fibrotic hypersensitivity pneumonitis (fHP), RA-ILD and SSc-ILD.

METHODS

Consecutive patients with a diagnosis of IPF, fibrotic hypersensitivity pneumonitis (fHP), rheumatoid arthritis associated ILD (RA-ILD) and Systemic Sclerosis associated ILD (SSc-ILD) presenting at the Royal Brompton Hospital (RBH) ILD Unit January 2010–December 2019 were considered for this retrospective study. The Ethics Committee of the Royal Brompton Hospital gave authorisation for the study (REC: 13/LO/0857). Adult participant consent was not required for institutional approval as the research was based on retrospective review of previously collected non-identifiable information. ILD diagnoses were made as per current guidelines.^{7–10} Baseline was defined as the date of the first lung function test performed at RBH. Only patients with CRP levels measured in the same laboratory by immunoturbidimetric assay (Beckman AU680 autoanalyser, Beckman coulter, UK), within 3 months of baseline were included in the study. Baseline anthropometric data, respiratory function and CRP levels were retrieved directly from the electronic database. Data on recent infections, within a month from CRP measurement, and medication, including antibiotic prophylaxis, at the time of sampling, were extracted from the clinical reports, written before any laboratory data (including CRP levels) was available. Patients with a recent infection were excluded from the study. Immunosuppressive treatment was defined as corticosteroid (prednisolone/methylprednisolone ≥ 1 mg/day) and/or other immunosuppressant agents (azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate and mycophenolate mofetil). All-cause mortality was collected until death, transplant, loss to follow-up or end of study period (December 31 2022).

Correlations, as well as mean and percentage differences, were estimated using generalized linear models using gaussian or binomial families, as appropriate. Multiple comparisons were corrected by Scheffé's method. CRP values below

SUMMARY AT A GLANCE

Little is known on links between serum CRP and outcome in interstitial lung diseases (ILD). We find that raised peripheral blood CRP levels are independently associated with mortality across a range of fibrotic ILDs and provide data to support future study design to identify ILD entity-specific CRP thresholds.

the detection level (< 1 mg/L) were analysed as 0.5 mg/L. CRP values were log transformed to reduce non-normality and to improve linearity of Martingale residuals in Cox regression analysis.¹¹ As a marker of ILD severity, the composite physiological index (CPI) was calculated as previously described.¹²

Survival analysis was performed using proportional Cox regression. Separate analyses were performed for each of the four disease groups. Confounders added in all multivariable analyses included age, smoking history (ever/never), gender, immunosuppressive treatment at the time of sampling and CPI, to adjust for disease severity. Additional analyses were performed utilizing forced vital capacity (FVC) and diffusion capacity of the lung for carbon dioxide (DLCO) in separate models. Proportionality of the hazard function over time was assessed using Nelson–Aalen cumulative hazard plots,¹³ and linearity of the proportional-hazards assumption of each covariate over time by analysis of Schoenfeld residuals. Preliminary analyses showed that cumulative hazards were reasonably linear for at least 5 years in all the disease groups, so this interval was selected for all the analyses (Figure S1 in the Supporting Information). Furthermore, we found that CPI (as well as the individual lung function parameters) violated the proportional hazard assumption, as the effect on survival was modest initially and started to increase after approximately 2 years. Accordingly, in the adjusted models, an interaction term between CPI and time > 2 years was added.¹¹ To compare the hazard ratios (HRs) for each of the different ILDs, the data from all four ILD entities was analysed in a single model which, in addition to the confounders listed above, included interaction terms between CRP and each disease group, with IPF as the reference. The data was also analysed using a threshold of CRP ≥ 5 mg/L, selected empirically because it corresponded to the geometric mean of the entire population, and as the threshold linked to mortality proposed in several studies of a number of disorders.^{5,14–16} Analyses were performed using the STATA 17.0 software (StataCorp, College Station, TX). A p -value of < 0.05 was considered significant.

RESULTS

Patients for whom CRP values were available at baseline, in the absence of recent infection, and with concomitant lung

TABLE 1 Baseline characteristics of the cohorts.

	IPF; <i>n</i> = 422	fHP; <i>n</i> = 233	RA-ILD; <i>n</i> = 111	SSc-ILD; <i>n</i> = 86
Age, years	71.9 (71.2–72.6) ^a	64.9 (63.6–66.2)	63.8 (61.6–66.0)	56.4 (53.4–59.3) ^a
Gender (Male (%))	82.0 (78.3–85.7) ^a	44.6 (38.3–51.0)	48.6 (39.4–57.9)	30.2 (20.5–39.9) ^a
Ethnicity (non-European (%))	13.6 (9.5–17.7) ^a	32.2 (25.9–38.5)	30.4 (21.8–38.9)	38.9 (28.5–49.0)
Smoking status (ever (%))	66.1 (61.6–70.6) ^a	36.5 (30.3–42.7)	57.7 (48.5–66.8)	41.9 (31.4–52.3)
CRP (mg/L)	4.2 (3.8–4.6)	4.3 (3.8–4.9)	7.8 (6.4–9.6) ^a	4.8 (3.9–5.9)
Baseline lung function				
DLCO % predicted	40.8 (39.5–42.1)	41.8 (40.0–43.6)	42.5 (39.3–45.6)	40.1 (37.3–42.8)
FVC % predicted	74.9 (73.2–76.6)	73.1 (70.3–76.0)	76.1 (72.2–80.0)	74.4 (70.4–78.3)
FEV1% predicted	79.8 (78.2–81.5) ^a	73.0 (70.2–75.8)	74.6 (70.8–78.3)	73.0 (69.5–76.5)
CPI	51.8 (50.7–53.0)	49.7 (48.0–51.3)	48.1 (45.2–51.0)	50.4 (47.9–52.9)
Immunosuppressive therapy	18.2 (14.6–21.9) ^a	38.4 (32.1–44.6)	73.0 (64.7–81.2) ^a	45.3 (34.8–55.9)

Note: CRP is shown as geometric mean (95% CI), all other data are presented as mean (95% CI) or percentage value (95% CI) as appropriate. Mean and percentage differences were estimated using generalized linear models using gaussian or binomial family as appropriate.

Abbreviations: CPI, composite physiological index; CRP, C-reactive protein; DLCO, diffusion capacity of the lung for carbon dioxide; FEV1, forced expiratory volume in 1 second; fHP, fibrotic hypersensitivity pneumonitis; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; SSc, systemic sclerosis.

^a*p* < 0.05.

function tests, included 422 with IPF, 233 with fHP, 111 with RA-ILD and 86 with SSc-ILD, corresponding respectively to 47%, 61%, 64% and 57% of the patients from each disease group present in the clinical database (Figure S2 in the Supporting Information). The baseline characteristics of the patients included in the study are shown in Table 1. Serum levels of CRP (geometric mean) were higher in RA-ILD (7.8 mg/L (95% CI: 6.4–9.6)) compared to the other groups (IPF: 4.2 mg/L (3.8–4.6), fHP: 4.3 mg/L (3.8–4.9), SSc-ILD: 4.8 mg/L (3.9–5.9)). Patients with IPF were older and more frequently male, of European descent, with a positive smoking history compared to the other disease groups, while patients with SSc-ILD were younger and less frequently male. Mean percent predicted FVC and DLCO, as well as CPI, were similar among the groups, while FEV1 was more preserved in IPF. The frequency of immunosuppressive treatment at the time of sampling was lowest in IPF and highest in RA-ILD.

To assess whether the study groups were representative of the larger patient populations in the clinical database, patients included in each disease cohort were compared to those excluded from the study. The only significant differences were that the IPF and RA-ILD patients included in the study were slightly younger than those excluded, and that fewer of the included fHP and SSc-ILD patients were on immunomodulatory therapy at baseline (Table S1 in the Supporting Information), while no significant differences were seen for gender, ethnicity, smoking history and lung function. In addition, survival did not differ between included and excluded patients in any of the four patient groups (Figure S3 in the Supporting Information).

The correlation coefficients of CRP levels with the confounders of interest in the four cohorts are presented in Table S3 in the Supporting Information. There was little correlation with most variables, except for baseline lung

function variables (FEV1, FVC, DLCO and CPI) in IPF, and for DLCO% predicted in SSc-ILD. Overall correlation (*R*-squared) of CRP with the five confounder variables included in all multivariable analyses (age, gender, smoking history, CPI and immunosuppressive therapy) was 0.04 in IPF, RA-ILD and SSc-ILD, and 0.03 in fHP.

The number of deaths during the first 5 years were: IPF *n* = 270 (64%), fHP *n* = 86 (37%), RA-ILD *n* = 51 (46%) and SSc-ILD *n* = 18 (21%). On univariable analysis, higher CRP levels were associated with worse survival in all four cohorts: IPF: HR (95% CI): 1.3 (1.2–1.6), *p* < 0.001, fHP: 1.6 (1.2–2.0), *p* < 0.001, RA-ILD: HR: 1.5 (1.2–2.0), *p* = 0.001 and SSc-ILD: 2.1 (1.3–3.2), *p* = 0.001). Survival analyses of the baseline demographics and measures of lung function are shown in Table S2 in the Supporting Information. On multivariable analysis including age, gender, smoking history, immunosuppressive therapy and CPI, CRP remained independently associated with survival in all four cohorts: IPF: HR (95% CI): 1.3 (1.1–1.5), *p* = 0.003, fHP: 1.5 (1.2–1.9), *p* = 0.001, RA-ILD: 1.4 (1.1–1.8), *p* = 0.01 and SSc-ILD: 2.7 (1.6–4.5), *p* < 0.001) (Table 2).

Multivariable models including DLCO or FVC, instead of CPI, gave substantially similar results (Table S4 in the Supporting Information), as did inclusion of the use of prophylactic antibiotics at sampling (Table S5 in the Supporting Information).

The relationship between CRP and mortality was strongest in SSc-ILD patients, as shown by a significantly higher HR for the interaction between disease cohort and CRP in SSc-ILD patients compared to the other groups, both on univariable and multivariable analyses (*p* = 0.05 and 0.003, respectively).

Patients with a CRP level of ≥5 mg/L were 48% of those with IPF, 47% with fHP, 69% of those with RA-ILD and 45% of those with SSc-ILD (50% overall). A CRP ≥5 mg/L

TABLE 2 Survival analysis.

	Univariable		Multivariable ^a	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
IPF	1.34 (1.15–1.56)	<0.001	1.27 (1.08–2.14)	0.003
fHP	1.55 (1.23–1.95)	<0.001	1.51 (1.19–1.92)	0.001
RA-ILD	1.54 (1.19–2.00)	0.001	1.41 (1.09–1.84)	0.01
SSc-ILD	2.08 (1.34–3.21)	0.001	2.73 (1.64–4.54)	<0.001

Abbreviations: fHP, fibrotic hypersensitivity pneumonitis; HR, hazard ratio; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; SSc, systemic sclerosis.

^aMultivariable analysis including age, gender, smoking history, immunosuppressive therapy and CPI.

TABLE 3 Survival analysis according to CRP ≥ 5 mg/L.

	Univariable		Multivariable ^a	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
IPF	1.58 (1.17–2.14)	0.003	1.50 (1.08–2.05)	0.01
fHP	2.33 (1.50–3.64)	<0.001	1.67 (1.05–2.65)	0.03
RA-ILD	2.43 (1.21–4.85)	0.01	2.66 (1.08–5.97)	0.02
SSc-ILD	3.80 (1.37–10.55)	0.01	4.63 (1.36–15.75)	0.01

Abbreviations: fHP, fibrotic hypersensitivity pneumonitis; HR, hazard ratio; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; SSc, systemic sclerosis.

^aMultivariable analysis including age, gender, smoking history, immunosuppressive therapy and CPI.

was associated with earlier mortality in all four disease groups on both univariable and multivariable models, with HR values shown in Table 3, and corresponding survival curves shown in Figure 1. The *R*-squared for the correlation between a CRP ≥ 5 mg/L and the other variables in the model was 0.05 in IPF and fHP, 0.06 in RA-ILD and 0.09 in SSc-ILD.

DISCUSSION

To our knowledge, this is the first study to report an association between CRP and survival across a range of ILDs. This could suggest common inflammatory pathways with an adverse impact on disease behaviour. Serum IL6, another acute phase protein which induces CRP synthesis, was associated with early mortality in patients with SSc-ILD.¹⁷ Elevated CRP has been associated with poor outcomes in cancer patients, regardless of cancer type¹⁸ and with increased risk of cardiovascular, cerebrovascular and all-cause mortality in hospital based cohorts,¹⁹ suggesting a non-specific lethal effect of an increased inflammatory systemic state, possibly related to regulation of the innate immune/inflammatory response. Interestingly, the strongest relationship between CRP and mortality was seen in SSc-ILD, while the weakest was seen in IPF, in keeping with the hypothesis that systemic inflammation plays a lesser role in IPF than in CTD-ILDs and fHP. An increased systemic

inflammatory state could contribute to reduced survival through a number of mechanisms, including involuntary weight loss, reduced functional status and cardiovascular disease, as observed in other chronic lung diseases such as COPD.^{20–22} Alternatively, although patients with physician-reported recent infection were excluded from the study, raised CRP levels could be a marker of (recurrent) subclinical infections, in turn linked to earlier mortality. Finally, CRP may have a direct pathogenic effect on the severity of lung tissue damage/aberrant wound healing by amplifying pre-existing inflammation and tissue injury.²³

Limitations of the study include its retrospective design, with clinical data extracted from patients' notes. This may have led to recent infections being under- or over-estimated. We excluded patients with recent infections at sampling because it is virtually impossible to distinguish the effects of infection from those of the underlying disease activity on both CRP levels and survival. Indeed, in the presence of recent infection, it would be impossible to interpret the levels of CRP in terms of disease activity. Furthermore, infections themselves could contribute to mortality both directly and indirectly, as a signal of decreased immune responses and worse general condition. We cannot exclude that raised CRP levels may have been in part linked to sub-clinical infections, which in turn could affect disease activity. In a retrospective cohort without a standardized protocol dedicated to evaluating frequency of infections, it is not possible to accurately quantify whether patients with higher baseline CRP may be more prone to more frequent infections and/or acute exacerbations over time. There is evidence that the abnormal microbiome observed in fibrotic ILD may influence the pathogenesis and progression of ILDs, with higher bacterial burden and reduced microbiome diversity linked to worse outcomes.²⁴ It is therefore possible that higher CRP levels could be an expression of greater lung dysbiosis. In future studies, it would be interesting to prospectively study potential links between CRP and the lung microbiome, as well as serial CRP measurements and incident infections against mortality.

The use of antibiotic prophylaxis in patients experiencing recurrent infections, might have affected the relationship between CRP and mortality. However, when the use of prophylactic antibiotics at the time of CRP sampling was included in multivariable analyses, the association between CRP and survival was unchanged in all four disease groups.

This study was conducted in a single centre and data on CRP were not available or had to be excluded, in approximately 40% of cases. However, the limited differences in baseline parameters and the similar survival rates between patients included and excluded from the study, reasonably reduce the possibility of significant selection bias. As serial CRP measurements were available only for a minority of patients, it was not possible to estimate the association between serial changes in CRP and mortality, or whether a fall in CRP in response to treatment was associated with improved survival.

RBH is a tertiary centre specialized in respiratory care, and patients seen at the ILD Unit could present with more

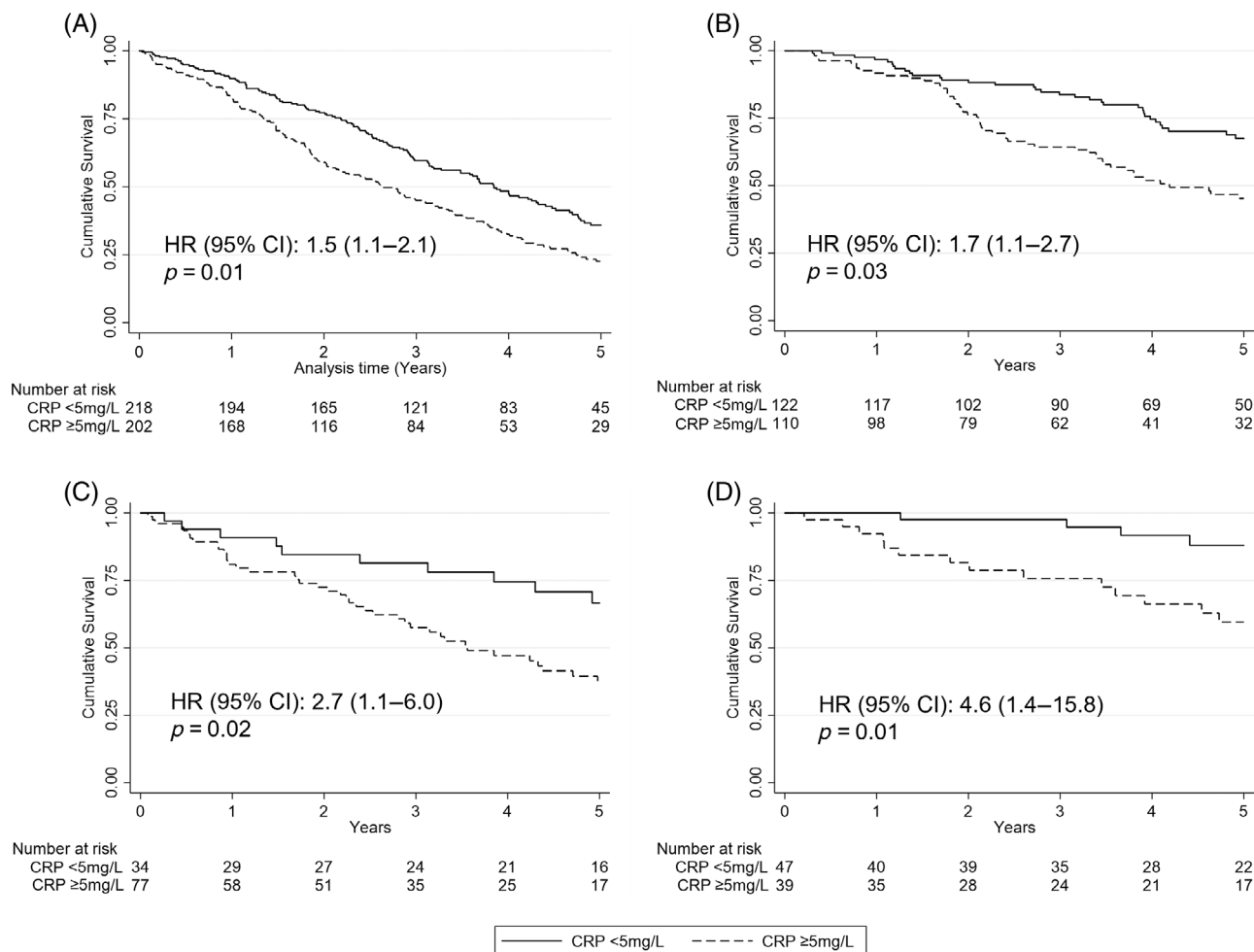


FIGURE 1 Survival according to CRP ≥ 5 mg/L. Kaplan–Meier survival analysis grouped by CRP ≥ 5 mg/L in the (A) IPF, (B) fHP, (C) RA-ILD and (D) SSc-ILD cohorts. HR and p -values shown are for multivariable analyses including age, gender, smoking history, immunosuppressive therapy and CPI.

severe disease, not fully representative of patients with similar diagnoses seen in different care settings. Nevertheless, the baseline characteristics of the cohorts are reasonably similar to those of recent prognostic and clinical trial studies.^{25–28} We cannot say whether the association between CRP and mortality applies to other ILD diagnoses. High sensitivity CRP was not measured routinely, and we are therefore unable to conclude whether it might provide stronger associations. Finally, specifically for IPF patients, there has been a change in management over the recruitment window to reduced immunosuppression use and introduction of antifibrotic therapy. We cannot exclude this being a factor affecting the results of this study in the IPF cohort.

The threshold of CRP ≥ 5 mg/L was selected empirically and should only be considered as a proof-of-concept. A CRP cutoff of ≥ 5 mg/L has been associated with adverse outcomes in several diseases. In 939 patients with angiography-proven cardiovascular disease, CRP ≥ 5 mg/L was independently associated with adverse 3 years cardiovascular outcome.¹⁴ CRP ≥ 5 mg/L on admission in 191 patients with acute myocardial infarction, was an

independent risk factor for reduced myocardial perfusion and mortality.¹⁵ Pre-renal transplant CRP ≥ 5 mg/L were associated with major cardiac events, more acute rejection episodes, and a lower 6 months survival in 459 patients.¹⁶ An enrollment criteria for the focuSSced trial of tocilizumab in SSc was that patients had to have elevated acute-phase reactant levels, including CRP ≥ 6 mg/L.²⁹ A CRP ≥ 5 mg/L was an independent predictor of mortality in 375 patients with SSc.⁵

This study was not designed to identify optimal CRP thresholds to be used as a prognostic biomarker in the individual ILD entities. We therefore cannot say whether CRP ≥ 5 mg/L is the best threshold for all four ILD entities included in this study, or whether different thresholds should be used in different diseases, as suggested by the fact that mean values were found to be greater in RA-ILD or considering the more pronounced prognostic association of CRP in SSc-ILD. The statistical power of a retrospective study such as this one depends heavily on the number of available patients, and we felt that the number of patients in each group was too small to address the selection of a clinically meaningful threshold for each ILD entity.

Furthermore, the fact that CRP levels are somewhat correlated with other variables of interest, such as respiratory function parameters, further contributes to reduce the statistical power. Given a squared multiple correlation coefficient (R^2) between a given CRP level and other predictors of around 0.05, and assuming a mortality rate of 50%, it would be necessary to recruit nearly 1000 patients in each ILD entity to assess a change in HR of 1.3 at a significance level of 0.05 with a power of 80%. It is therefore important that this data is replicated in other patient populations before it can be interpreted clinically. The present study provides useful data to support the design of studies to prospectively evaluate optimal prognostic CRP thresholds in each ILD entity.

In conclusion, the link between serum CRP and earlier mortality across IPF, fHP, RA-ILD and SSc-ILD, is an interesting finding with potential pathogenetic implications requiring further study. Replication in independent prospective cohorts is required to confirm our findings, and to identify potential clinically applicable CRP thresholds to provide prognostic separation.

AUTHOR CONTRIBUTIONS

Carmel J. W. Stock: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **William G. Bray:** Data curation (equal); formal analysis (equal); investigation (equal); writing – review and editing (equal). **Vasilis Kouranos:** Data curation (equal); writing – review and editing (equal). **Joseph Jacob:** Data curation (equal); writing – review and editing (equal). **Maria Kokosi:** Data curation (equal); writing – review and editing (equal). **Peter M. George:** Data curation (equal); writing – review and editing (equal). **Felix Chua:** Data curation (equal); writing – review and editing (equal). **Athol U. Wells:** Data curation (equal); writing – review and editing (equal). **Piersante Sestini:** Formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Elisabetta A. Renzoni:** Conceptualization (equal); investigation (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

Vasilis Kouranos reports lecture fees from Novartis and Boehringer Ingelheim. Joseph Jacob reports consulting fees from Boehringer Ingelheim, Roche, GlaxoSmithKline and NHSX, lecture fees from Boehringer Ingelheim, Roche, GlaxoSmithKline and Takeda, advisory board fees from Boehringer Ingelheim, and Roche, conference attendance support from Boehringer Ingelheim, and UK patent application numbers 2113765.8 and GB2211487.0. Peter M. George

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Elisabetta Renzoni is an Associate Editor at Respirology and a co-author of this article. Elisabetta Renzoni was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

HUMAN ETHICS APPROVAL STATEMENT

This study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the Royal Brompton Hospital gave authorisation for the study (REC: 13/LO/0857). Adult participant consent was not required for institutional approval as the research was based on retrospective review of previously collected non-identifiable information.

ORCID

Carmel J. W. Stock  <https://orcid.org/0000-0003-4090-8761>

Felix Chua  <https://orcid.org/0000-0001-7845-0173>

Athol U. Wells  <https://orcid.org/0000-0003-2108-6248>

Elisabetta A. Renzoni  <https://orcid.org/0000-0002-1118-797X>

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SUPPORTING INFORMATION

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

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