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Original research article

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Please cite this article as: Achaiah A, Lyon P, Fraser E, *et al*. Increased monocyte level is a risk factor for radiological progression in patients with early fibrotic ILA. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00226-2022).

Increased monocyte level is a risk factor for radiological progression in patients with early fibrotic ILA

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Acknowledgement
The study was funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). LPH is supported in part by the MRC UK (MC_UU_00008/1). Correspondence to Prof Ling-Pei Ho (ling-pei.ho@imm.ox.ac.uk).

Authors contribution
AA conceived project, conducted analysis, interpreted data, and wrote the paper. PL performed ILA search and collated data. EF, PS and RH provided guidance with project. RB provided guidance with project and assisted with defining search criteria. LPH conceived project, interpreted data, wrote paper, and supervised the study.

Conflict of interest disclosures:
Andrew Achaiah, Paul Lyon, Emily Fraser, Rachel Benamore, Ling-Pei Ho and Rachel Hoyles report no relevant conflict of interests. Peter Saunders has received consultancy fees from Trevi Therapeutics, and lecture fees from Boehringer Ingelheim, but no other conflict of interest.

Words 3428

Abstract

Background

Interstitial lung abnormalities (ILA) are specific spatial patterns on computed tomography scan (CT), potentially compatible with early interstitial lung disease (ILD). A proportion will progress; management involves risk stratification and surveillance. Elevated blood monocyte levels have been shown to associate with progression of IPF.

Aims

To (i) estimate the proportion of "early fibrotic" ILAs (EF-ILA; reticular +/- ground glass opacities, excluding traction bronchiectasis and honeycombing) on CTs of patients attending all-indications thoracic CTs, and proportion demonstrating radiological progression and (ii) explore association between peripheral blood leukocyte levels and ILA progression.

Methods

We analysed all thoracic CT reports in individuals aged 45-75 performed between January-2015 and December-2020 in one large teaching hospital (Oxford, UK) to identify patient CT reports consistent with EF-ILA. CT-contemporaneous blood leukocyte counts were examined to explore contribution to progression and all-cause mortality, using multivariate Cox regression.

Results

40,711 patients underwent thoracic CT imaging during this period. 1259 (3.1%) demonstrated the EF-ILA pattern. Mean age; 65.4 (±7.32), male; 735 (47.8%). EF-ILA was significantly associated with all-cause mortality [HR 1.87, 95%CI 1.25-2.78, p=0.002].

362 cases underwent at least one follow-on CT. Radiological progression was observed in 157 cases (43.4%); increase in reticulation; 51, new traction bronchiectasis; 84, and honeycombing; 22. Monocyte count, neutrophil count, monocyte:lymphocyte ratio, neutrophil:lymphocyte ratio and 'systemic inflammatory response index' were significantly associated with radiological progression.

Conclusion

3.1% of subjects requiring thoracic CT during a 6-year period demonstrated EF-ILA. Monocyte levels, and blood leukocyte-derived indexes were associated with radiological progression and could indicate which patients may require closer follow up.

Introduction

Interstitial lung abnormalities (ILA) refers to specific spatial patterns on computed tomography (CT) scan that are potentially compatible with interstitial lung disease (ILD) in individuals where ILD was not previously suspected.[1] As a proportion of ILAs are detected coincidentally in asymptomatic individuals, it is difficult to determine its prevalence. However large cohort studies have reported prevalence of 2-10%,[2-5] and a higher risk of mortality.[2,6] ILAs have been shown to be associated with symptoms including breathlessness, reductions in lung function,[2] and exercise capacity,[7] and genetic abnormalities common to familial interstitial pneumonia and idiopathic pulmonary fibrosis (IPF). [8,9] A proportion of ILAs are known to progress to IPF, yet ILA prevalence exceeds that of IPF by considerable margin. Therefore identifying cases at risk of progression is an important clinical priority.[10]

Future implementation of lung cancer screening and greater use of CT imaging for other diagnostic purposes are likely to increase detection of ILA and pose resource implication for ILD services.[11] A recent position paper on ILA from the Fleischner Society discussed risk stratification, schema for follow-up evaluation and the importance of subcategorising for the subpleural fibrotic ILA, which has greater mortality risk.[1]

Earlier detection of fibrotic ILAs could lead to a shorter lag time to ILD diagnosis, potentially allowing earlier treatment intervention and improved patient outcome.[12] Perhaps more pressing is a need for an easily accessible test to stratify patients to those who are more likely to progress and therefore require follow up.

Measurement of peripheral blood leukocytes for prognosis purposes in IPF has gained interest in recent years.[13-15] Furthermore, indexes derived separately from peripheral blood leukocytes have demonstrated correlation with adverse clinical outcomes in ILD.[16]

In this study, we examined the prevalence of ILA with early fibrotic features in a population over a six-year period. Focusing on radiographic appearances, we identified a group of ILAs, which we termed 'early fibrotic ILA' defined as those with reticular +/- ground glass presence and excluding traction bronchiectasis and honeycombing; and questioned if there is an association between leukocyte profile and outcome, focusing on mortality, and radiological progression (in extent, and with emergence of traction bronchiectasis and honeycombing).[17]

Methods

Using the UK National Health Service-based Clinical Record Interactive Search (CRIS) database of the Oxford University Hospitals NHS trust (estimated catchment population of 800,000, Oxfordshire, UK), we examined available CT reports for all thorax-protocolised CT scans performed between January-2015 and December-2020. We performed a starting key word search using criteria selective for parenchymal abnormalities with an early fibrotic pattern – ["reticulation" or "interstitial"] AND ["sub-pleural" or "basal" or "lower zone" or "Possible UIP"] AND [Age range: 45-75]. Further details are provided in supplementary methods.

We then screened the preliminary search for additional radiographic features – ground glass opacities (GGO), traction bronchiectasis, honeycombing in acknowledgment that multiple parenchymal features can co-exist on CT.[1,18] Cases with or without GGO, but without traction bronchiectasis and honeycombing were termed 'early fibrotic ILA' (EF-ILA). Those with traction bronchiectasis and honeycombing were classified as CTs showing traction bronchiectasis and/or honeycombing. We considered that these were representative of established fibrosis and/or UIP pattern fibrosis, and not ILAs. In a proportion of cases identified from the preliminary key word search, we later found on screening that CT reports were detailing negative / absence of specific

radiological patterns – these were defined as a ‘ Nil ILA’ reference cohort. These cases were separated from the EF-ILA cohort.

Demographic data were collated, including age, gender, and comorbidity profiles.

Over this period, patients who had more than one CT scans were identified, and the reports of the earliest and latest CT scan analysed for radiographic progression. Radiographic progression was recorded as a binary event. It was defined as increase in either extent of identified early fibrotic features (reticulation and or GGO), new emergence of traction bronchiectasis, and/or new emergence of honeycombing. In cases not demonstrating radiographic progression, this was defined as unchanged pre-existing parenchymal features and absence of new features. Time interval between first and latest CT was calculated. Mortality was recorded and time from first CT was calculated. For those that survived, a censoring date of 1.4.2021 was used.

Blood leukocyte counts (monocyte, neutrophil, and lymphocytes) closest to the CT scan were recorded and monocyte:lymphocyte ratio (MLR), neutrophil:lymphocyte ratio (NLR) and systemic inflammatory response (SIRI; Monocytes x Neutrophils) ÷ Lymphocytes) indexes were calculated.[19]

Statistical analysis

Where relevant, tests for normality of data were performed using a D'Agostino & Pearson test and following this the difference between groups was analysed using unpaired t-tests or Mann-Whitney test for respective parametric and non-parametric analysis. Contingency tests (Fisher’s exact test of significance) were used to assess categorical data.

Cox proportional hazard models were used to determine hazard ratios (HRs) to progression and all-cause mortality (separate models). In both models, age, gender, monocytes, neutrophils, and lymphocytes levels obtained at a time point closest to the CT scan were included. CoV values for each case were calculated from available counts for monocyte, neutrophil, and lymphocytes (and derived indexes) in the 1 year up to first CT to account for within-group variance in these measures. ILA categories were included in regression models and where stated hazard ratios represent either absolute floating risk or expressed relative to the "nil ILA" category (reference category). Hazard ratios generated from continuous covariates represented the change in the risk of outcome if the covariate in question changes by one unit. Statistical significance was performed using the likelihood ratio test.

Reported statistical confidence intervals (CI) are at 95%. Two-tailed p values <0.05 determined statistical significance. All analyses were performed using Graphpad Prism (version 9) or SPSS version 26 (IBM Armonk, NY, USA).

Ethical approval

The study was part of a study to examine the factors associated with disease progression in IPF (ethical approval 14/SC/1060 from the Health Research Authority and South-Central National Research Ethics Service).

Results

CT-based patient categorisation and demographics

170,197 CT scans were performed that included any thoracic CT protocol between January 2015 and December 2020 in 40,711 patients. 3987 CT scans (performed in 2735 patients) satisfied the starting search criteria of ["reticulation" or "interstitial"] AND ["sub-pleural" or "basal" or "lower zone" or

"Possible UIP"] AND [Age range: 45-75]. 355 cases did not demonstrate ILD or ILA and were used as a non-ILA reference cohort. 762 cases also demonstrated additional traction bronchiectasis and or honeycombing present on their first CT. 490 cases demonstrated traction bronchiectasis only, 270 demonstrated honeycombing +/- traction bronchiectasis.

1259 (3.1% of 40,711) cases demonstrated reticulation +/- GGO, without traction bronchiectasis or honeycombing. 430 also had emphysema and 88 also had non-emphysematous cysts . Therefore, 3.1% of subjects (1259 of the starting cohort of 40,711) requiring thoracic CT between 2015-2020 demonstrated 'EF-ILA'. Mean age of the EF- ILA was 65.4 (±7.32); male; 735 (47.8%).

Demographic profiles are listed in Table 1 and a flow chart of ILA features and progression listed in Figure 1. Comorbidity profiles were identified by cross referencing electronic health records. Comorbidities are representative at time search was conducted and not at time of first CT.

3217 CT scans (80.7% of scans with available information) were reported by a thoracic radiologist.
343 cases with EF-ILA on first CT were seen in ILD clinic. Mean time from CT to clinic attendance was 3.1 years.

Radiological progression on follow on CT

Of the 1259 cases with EF-ILA, 362 patients underwent at least one follow-on CT scan, allowing examination of radiological change. Median time interval between CTs was 0.83 years (inter-quartile range 0.32-1.95). Progression in type or extent of ILA was observed in 157 cases (43.4%). Of these, increase in reticulation was observed in 51 cases (14.1% of 362). Progression with emergence of traction bronchiectasis (excluding honeycombing) was observed in 84 cases and (23.2%) and honeycombing (with or without traction bronchiectasis) in 22 (6.1%). 205 (56.6%) did not progress during this time (up to 5 years).

Median time interval between CT scans in cases demonstrating progression was 1.24 years (IQR 0.53-2.36, maximum 5.20) vs 0.59 years (0.27–1.19, maximum 5.05) in cases demonstrating no progression. ($p<0.001$).

Not surprisingly, multivariate Cox regression analysis showed that radiographic progression of EF-ILA was associated with mortality [HR 1.92, 95%CI 1.51-3.21, p=0.013].

Imaging features and ILA mortality

Death was reported in 448 cases (16.40%) in the six years of analysis. Mean time from first CT to death was 19.8 ±16.5 months vs 35.6 ±20.6 in those that survived ($p<0.0001$). In cases with the early fibrotic ILA, death was reported in 183 cases. Mean time from first CT to death was 19.0 ±16.6 months vs 32.7 ±20.5 in those that survived.

Association between specific ILA features noted on first CT and mortality was explored using multivariate Cox regression (Table 2). As expected, traction bronchiectasis [HR 2.09, 95%CI 1.36-3.20, p=0.0001] and honeycombing [HR 3.65, 2.38-5.60, $p<0.0001$] were significantly associated with mortality relative to the Nil ILA reference category. Cases with the EF- ILA also demonstrated significant mortality risk [HR 1.87, 1.25-2.78, p=0.002]. This risk was slightly higher in cases of EF-ILA that also demonstrated GGO [HR 2.03, 1.29-3.19, p=0.002] in comparison to cases of EF-ILA without GGO [HR 1.80, 1.19-2.72, p=0.005]. Mortality risk of EF-ILA was preserved when adjusting for the respiratory comorbidities; lung cancer, pneumonia, and COPD/emphysema. Lung cancer and pneumonia were also significantly associated with mortality in the EF-ILA group (see Suppl table S1).

Blood leukocyte association with radiological progression of ILA and mortality

We explored association between peripheral blood leukocytes and their derived leukocyte indexes against radiographic progression and mortality using multivariate Cox proportional hazards models (Table 3). All models included age, gender, and the leukocyte values (or their derived indexes) contemporaneous with CT scan. Where stated leukocyte co-efficient of variation (CoV) of each leukocyte type over the year leading to the CT was included in multivariate models. Nearest available blood measurement of monocyte, neutrophil, and lymphocyte to first CT scan were obtained from standardised hospital 'full blood count' measurements. Median time interval between CT and nearest blood sampling was 1 day (IQR -13 to 30).

In the 362 cases of EF-ILA that underwent at least 2 CT scans, monocyte count [HR 1.79 1.05-2.86, p=0.030] and Neutrophil count [HR 1.11, 1.02-1.29, p=0.009], MLR [HR 2.28, 1.33-3.87, p=0.002], NLR [HR 1.07, 1.01-1.14, p=0.024] and SIRI [HR 1.09, 1.04-1.14, p=0.0002] were significantly associated with radiographic progression of the early fibrotic ILA on multivariate Cox regression analysis. (Table 3 and Table 4). Higher monocyte count, MLR, NLR and SIRI remained significant, when adjusting for respiratory co-morbidities (lung cancer, pneumonia and COPD/emphysema) in this cohort. Neutrophil count continued to show similar direction of effect towards progression but was not significant (Suppl Table S2 and S3).

In the 1259 cases demonstrating EF-ILA on first CT, monocyte count [HR 1.12, 1.01-1.36, p=0.003], neutrophil count [1.13, 1.07-1.19, p<0.001] and all their derived indexes were significantly associated with all-cause mortality. MLR; [1.16, 1.02-1.31, p=0.025], NLR; [1.07, 1.05-1.09,p<0.001] and SIRI [1.06, 1.04-1.08, p<0.001] (Table 3 and 4). Mortality risk was preserved in all in models adjusting for respiratory comorbidity, except for monocytes (Suppl Table S2 and S3).

In separate regression models coefficient of variation (CoV) of longitudinal measurements for each leukocyte / index was also included, to adjust for any effect that variation in longitudinal measurement of these leukocyte parameters may have on clinical outcome. Monocytes maintained significant hazard towards both mortality and progression of EF-ILA (see Suppl Table S4). Distribution of leukocyte levels and their derived indexes are shown in Suppl Fig 1.

Discussion

This study shows that in an unselected cohort of patients undergoing thoracic CT scanning for all indications, in a 6-year period, 3.1% of patients showed evidence of 'early fibrotic ILA'. In a subset which have more than one CT scan during this 6-year period, 43% progressed in extent of disease or demonstrated new traction bronchiectasis or honeycombing. Monocytes, monocyte:lymphocyte ratio, neutrophil:lymphocyte ratio and SIRI were associated with progression in a multivariate analysis which included analysis of age and gender.

Our findings are comparable to ILA prevalence observed in large population-based cohorts[2,3,20] and lung cancer screening cohorts[21,22] in which ILA ranged between 3-10%. Our definition of 'early fibrotic ILA' which include reticulation and GGO but not traction bronchiectasis and honeycombing probably encompass 'indeterminate UIP' as defined in the 2018 IPF guidelines.[17] However, as we are unable to assess CT distribution of these ILA in all cases for this large cohort, the terminology of early fibrotic ILA was used. Since reticular abnormalities are common in older individuals and have previously been regarded as part of the normal spectrum of senescent lung,[23] we limited inclusion to individuals aged 45-75 at time of CT.[24] Comparable to other studies, gender was roughly of equal proportions across all cases in this cohort in those with 'early fibrotic ILA', where traction bronchiectasis and honeycombing were excluded.[2,3]

The AGES[3] and Framingham[2] population-based studies demonstrated ILA progression in 43% and 64% of cases, with associated risk of mortality which is also similar to our cohort. In AGES, prevalence of indeterminate for UIP (iUIP) was estimated at 3.9%. iUIP was associated with mortality risk in univariate analysis [HR 1.6, p<0.0001] but not significantly in multivariate analysis [HR 1.2, p=0.07]. In our cohort, with a much higher number of cases, multivariate analysis showed that early fibrotic ILA is associated with all-cause mortality [HR 1.87, p=0.002].

Importantly, we and others,[6] demonstrate radiographic progression is not observed in the majority of cases. It remains challenging to predict those cases that will progress to established fibrotic ILD. To address this, the Fleischner society recently proposed a schema to facilitate triage, management and follow up of ILAs.[1] This includes sub-categorising cases according to ILA distribution on CT and presence (or absence) of ILAs indicative of established fibrosis.

ILA assessment in individuals with a history of familial interstitial lung disease has identified association with particulate exposures, age, positive smoking history and shorter telomere length and MUC5b risk allele.[25,26] Associations among ageing-related biomarkers and ILA have been explored,[27] however collectively these are costly and are not routinely available for large scale use. Furthermore, with implementation of routine lung cancer screening pathways and greater use of thoracic CT for other diagnostic purposes it is anticipated that ILA detection will increase. Patient follow-up could have a huge implication on clinical resources.

Peripheral blood leukocyte measure is available as part of routine full blood count analysis and integrating this simple and cheap measure into risk stratification and ILA management is worthy of future consideration. This is supported by studies in IPF patients where elevated peripheral blood monocyte count has been shown to be predictive of disease progression and mortality. The study by Scott et al, a large multicentre retrospective cohort study, first demonstrated that monocyte count $\geq 0.95 \times 10^9$/l were associated with all-cause mortality in IPF and non-IPF fibrotic lung disease.[13] Since then other retrospective clinical studies have documented similar findings.[14,15,28] In an analysis of multiple independent cohorts (MESA, AGES, COPDGene, and ECLIPSE; n=7396) Kim et al report association between higher absolute monocyte count and ILA progression.[29]

There are subtle, but important difference between our study and Kim et al, who report the findings of a pooled analysis of four population-based cohorts (two COPD-focused cohorts). In this heterogenous population, Kim et al do not discuss if their observed association between monocytes and ILA progression is limited to specific ILAs, such as those with early evidence of fibrosis. In our study the inclusion criteria were biased towards selection of cases with CT features potentially compatible with early fibrosis, thus population-based enriched for patients potentially at risk of progressing to pulmonary fibrosis.[1] In our cohort of progressors, we detail the proportion of cases with new CT features representative of established pulmonary fibrosis and report association between absolute monocyte count (and other leukocyte parameters) with progression and all-cause mortality. We also adopted a different approach to data analysis, employing Cox proportional hazards modelling to take account of time until events occurred.

Mechanistically, our findings, could be explained by recent experimental evidence suggesting migration of monocytes from bone marrow to injured lung, then differentiating into macrophages with a pro-fibrotic phenotype.[30] Further support comes from translational studies that implicate distinct monocyte-derived alveolar macrophage populations in progression of fibrosis.[31,32]

Other studies have also implicated neutrophils and lymphocytes in pulmonary fibrosis. Akin to monocytes, neutrophils are recruited to areas of inflammation.[33] Similar to macrophages, they can alter their microenvironment by secreting proteases, oxidants, cytokines, and chemokines.[34]

Neutrophils are also a substantial source of matrix metalloproteinases (MMP) which are involved in collagen deposition and Extra-cellular matrix formation.[35] Neutrophilic bronchoalveolar lavage (BAL) specimens taken from patients with IPF has been associated with early mortality.[36]

We have previously demonstrated in a cohort of patients with CTs demonstrating the indeterminate for UIP that peripheral blood monocyte and neutrophil counts are implicated progression to IPF,[37] and association of NLR, MLR and SIRI with mortality in IPF.[38] MLR has been primarily used to prognosticate in cancer studies in recognition that host systemic inflammatory responses have influence on tumour proliferation and disease progression.[39] NLR has been heavily studied as a systemic inflammatory marker.[40] It has been used to prognosticate systemic inflammatory diseases such as rheumatoid arthritis,[41] and recently in connective tissue disease-related ILD and IPF.[16] The systemic inflammation response index (SIRI), integrates neutrophils, monocytes, and lymphocytes into one composite measure and has shown promise as a prognosticator within oncology.[19]

There are several limitations that should be considered when interpreting these results. We were unable to quantify extent of disease and extent of progression. Categorisation was based on qualitative information extracted from radiology reports and does not quantify individual ILA extent which may contribute to rate of progression. Similarly, we were unable to capture indication for CT and we cannot account for clinical symptoms, which would have been interesting to explore. Therefore, interpretation of our findings is limited to association between CT features with blood leukocytes. The patients were also selected because of their need for a thoracic CT, so the true prevalence in the population is unknown, only in those who requires a thoracic CT. In the group where we assessed progression, the interval between the first and last CT was longer in those who progressed compared to those who did not. It could be argued that those who did not progressed would do so over a longer period of assessment. The 'Nil ILA' group was identified by description of negative findings of key words from CT reports (e.g. "no reticulation"). We acknowledge that this represents a smaller proportion of patients with normal CT scans and may have introduced bias to EF-ILA mortality risk calculation. However, selection criteria were identical and demographic and comorbidity profiles were comparable between Nil ILA and EF-ILA group. Furthermore demographic profiles of the Nil-ILA group are also comparable to the 'Nil ILA' cohorts of other longitudinal studies.[3]

A proportion of our EF-ILA cohort were subsequently seen in our ILD clinic. Mean time from first CT scan demonstrating EF-ILA to ILD clinic attendance was +3.1 years. As the ILD clinic was a first-attender clinic, it is likely (but not verified) that these were patients who became symptomatic or demonstrated progression after a follow-on CT scan and did not have a prior diagnosis if ILD. There is therefore possibility of prior undiagnosed ILD. Under-reporting of ILA has previously been described.[42] As such we cannot exclude the possibility that a degree of misclassification may have occurred. However, 80.7% of CT scans were reported by post radiology fellowship specialist thoracic radiologists who attend interstitial lung disease multi-disciplinary team meetings, and based at a single centre which might mitigate inter-observer difference. Excellent inter-observer correlation between our thoracic radiologists in reporting ILD features ($r=0.91$; $p<0.001$) has previously been described.[43] The remaining 19.3% of CTs were reported by 1 of 14 Oxford-based post training radiologists. All radiologists collectively agree on descriptive reporting phrases and there are regular local discrepancy meetings to check on accuracy of reporting.

World Health Organisation International classification of diseases version 10 (ICD-10) coding was used to identify comorbidity during the 6 years of study follow up, but without coding dates we were unable to align comorbidity events to 1st CT scan date. Smoking history was poorly captured using 'ICD-10 coding'. We therefore elected not to include this information in our multivariate analysis but acknowledge that patients who smoked may show a greater rate of ILA progression. Finally, the

single-centre and retrospective nature of this study should be taken forward by prospective, intervention and validation studies in a different cohort.

Notwithstanding these limitations, our study, in a very large cohort with high proportion of specialist thoracic-radiologist reporting, demonstrates that monocyte levels, MLR, NLR and SIRI are associated with progression in early fibrotic ILA. Further in prospective studies will help determine if these parameters could be used to help prioritise patients who might benefit from follow up.

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Tables

Table 1

Patient characteristics	No ILA	Early fibrotic ILA
Demographics		
Female (%)	152 (42.8%)	657 (52.2%)
Male	203 (57.2%)	602 (47.8%)
AGE at first CT (SD)	63.4 (8.1)	65.39 (7.32)
Comorbidity		
COPD / Emphysema	52 (14.6%)	306 (19.9%)
Pneumonia	70 (19.7%)	344 (22.4%)
Lung cancer	30 (8.5%)	183 (11.9%)
Pulmonary hypertension	13 (3.7%)	68 (4.4%)
T2DM	57 (16.1%)	259 (16.8%)
Hypertension	172 (48.5%)	664 (43.2%)
IHD	66 (18.6%)	289 (18.8%)
Cardiomyopathy	115 (32.4%)	412 (26.8%)
Blood leukocyte measurements		
Time from CT to nearest Blood test (months):		
Mean	0.87 (5.92)	0.78 (6.29)
Median	0.11 (-0.23 to 1.24)	0.10 (-0.39 to 1.11)
Monocyte ($1x10^9$/l)	0.65 (0.29)	0.67 (0.31)
Neutrophil ($1x10^9$/l)	5.46 (3.30)	5.24 (3.00)
Lymphocyte ($1x10^9$/l)	1.76 (0.92)	1.94 (3.60)
MLR	0.46 (0.39)	0.45 (0.36)
NLR	4.46 (5.79)	3.92 (5.22)
SIRI	3.21 (5.74)	2.75 (4.33)
Seen in ILD clinic	38 (10.7%)	343 (27.2%)
Length of follow up (months)	21.46 (21.7)	23.4 (21.8)
Time from 1st CT to ILD clinic visit	16.75 (16.8)	37.4 (160.9)

Table 1. Demographic and blood leukocyte profiles of all patients, nil ILA, early and established interstitial lung disease. MLR; monocyte:lymphocyte ratio. NLR; Neutrophil:lymphocyte ratio. SIRI; [(Monocytes x Neutrophils) ÷ Lymphocytes]. T2DM - type 2 diabetes mellitus, IHD - ischaemic heart disease, ILD - interstitial lung disease. Continuous values expressed as mean (standard deviation) unless stated.

Table 2

Covariate	n (%)	Death (%)	HR (95% CI)	Sig.
Age	--	--	1.02 (1.01-1.04)	0.010*
Gender (Male)	1486 (54.3%)	268 (18.0%)	1.11 (0.91-1.36)	0.295
Nil ILA (reference)	355 (12.9%)	43 (12.1%)	--	--
Early fibrotic ILA	1259 (46.0%)	183 (14.5%)	1.87 (1.25-2.78)	0.002*
TBx without Honeycombing	490 (17.9%)	86 (17.6%)	2.09 (1.36-3.20)	0.0001*
Honeycombing +/- TBx	272 (9.9%)	87 (32.0%)	3.65 (2.38-5.60)	<0.0001*

Table 2. Multivariate Cox regression examining association of ILA features on first CT scan with mortality. Hazard ratios (HR) for ILA categories representative of risk relative to Nil ILA reference category. TBx; Traction bronchiectasis, EF-ILA; Early-fibrotic ILA. Findings were similar when adjusted for respiratory co-morbidities (Suppl Table S1).

Table 3

Covariates	Mortality HR (95% CI)	Sig.	Radiological progression HR (95% CI)	Sig.
-Age	1.03 (1.01-1.06)	0.005*	1.03 (1.00-1.06)	0.027*
-Gender	1.04 (0.76-1.42)	0.811	0.92 (0.67-1.27)	0.609
-Monocytes ($1x10^9$/l)	1.12 (1.01-1.36)	0.003*	1.79 (1.05-2.86)	0.030*
-Neutrophils ($1x10^9$/l)	1.13 (1.07-1.19)	<0.001*	1.11 (1.02-1.29)	0.009*
-Lymphocytes ($1x10^9$/l)	0.97 (0.85-1.09)	0.574	0.99 (0.94-1.04)	0.596

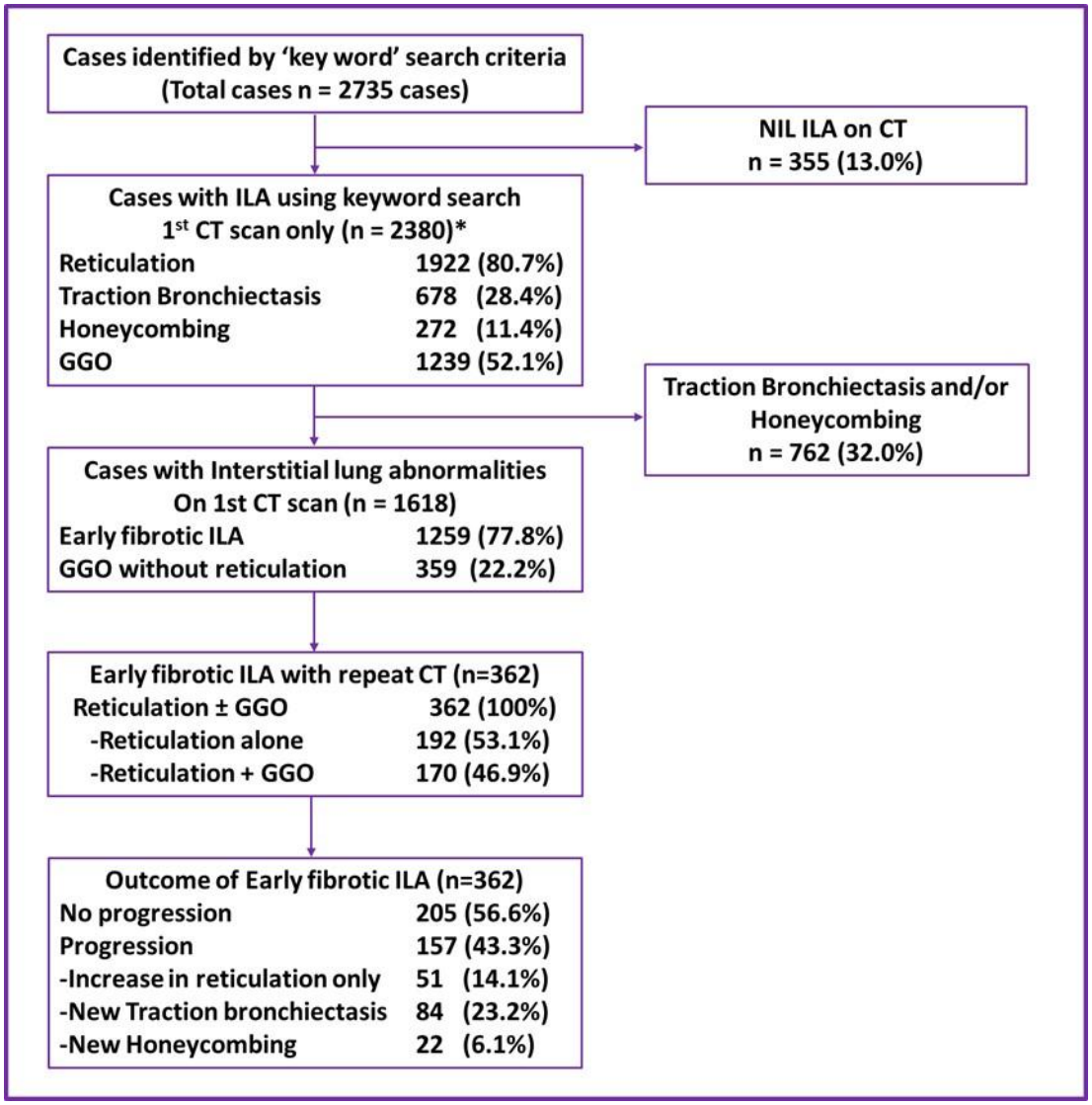
Table 3 Multivariate cox regression examining association between blood leukocyte and (i) mortality in "early fibrotic" ILA (n=1259) and (ii) radiological progression in "early fibrotic" ILA cohort with available repeat CT for comparison (n=362). When adjusting for respiratory co-morbidities, monocytes remained independently associated with progression (Suppl Table S2).

Table 4

Covariates	Mortality HR (95% CI)	Sig.	Radiological progression HR (95% CI)	Sig.
MLR				
-Age	1.03 (1.01-1.06)	0.006*	1.02 (0.99-1.05)	0.113
-Gender	1.00 (0.74-1.36)	0.995	0.92 (0.67-1.27)	0.624
-MLR	1.16 (1.02-1.31)	0.025*	2.28 (1.33-3.87)	0.002*
NLR				
-Age	1.03 (1.01-1.06)	0.007*	1.02 (0.99-1.05)	0.122
-Gender	0.98 (0.72-1.34)	0.910	0.96 (0.70-1.32)	0.814
-NLR	1.07 (1.05-1.09)	<0.0001*	1.07 (1.01-1.14)	0.024*
SIRI				
-Age	1.04 (1.01-1.06)	0.003*	1.03 (0.99-1.05)	0.079*
-Gender	1.02 (0.75-1.38)	0.924	0.96 (0.69-1.31)	0.789
-SIRI	1.06 (1.04-1.08)	<0.0001*	1.09 (1.04-1.14)	0.0002*

Table 4 Multivariate cox regression examining association between blood leukocyte indexes and (i) mortality in "early fibrotic" ILA (n=1259) and (ii) radiological progression in "early fibrotic" ILA cohort with available repeat CT for comparison (n=362). Each leukocyte index, age and gender is a separate model. MLR; monocyte:lymphocyte ratio. NLR; Neutrophil:lymphocyte ratio. SIRI; [(Monocytes x Neutrophils) ÷ Lymphocytes]. Similar findings were observed when leukocyte indexes were adjusted for respiratory comorbidity and when adjusted for coefficient of variation over a year (see suppl Table S3 and S4).

Figure 1. Flow diagram of ILA features and radiological progression of cases with the early fibrotic ILA. Where more than one CT scans were performed during the observation period, the first CT scan (1st CT scan) was used as the CT scan for the patient. *A proportion of first CTs demonstrated 2 or more ILA features simultaneously.



Supplementary materials

Description of methods

Search Criteria and data collation

The Clinical Record Interactive Search (CRIS) database of the Oxford University Hospitals NHS trust was used to search for reports for all thorax-protocolised CT scans performed between January-2015 and December-2020. The search was conducted in two phases. In phase 1, search criteria were selective for the early fibrotic ILA radiological pattern which we defined as reticulation in absence of traction bronchiectasis and honeycomb formation. Search criteria is as follows:

["reticulation" or "interstitial"]
AND
["sub-pleural" or "basal" or "lower zone" or "Possible UIP"]
AND
[Age range: 45-75]

Search criteria were defined with close guidance from our lead thoracic radiologist (RB) based upon the vocabulary tendencies of our thoracic radiologists when reporting CTs. We defined upper limit of age as 75 years.[1] Reticular abnormalities are common in older individuals and have sometimes been regarded as part of the normal spectrum of senescent lung.[2] Reporting findings as such could downgrade its clinical significance and introduce ambiguity to this dataset.[3] Possible UIP was included in search criteria as this term, used in the 2011 iteration of the IPF guideline, can also include reticulation in absence of traction bronchiectasis and distinct absence of honeycombing.[4] Fibrotic ILAs with basal and peripheral predominance are considered to possess greater risk of progression and mortality. As such this distribution was also incorporated into the search criteria in an “OR” rather than “AND” fashion. This was to maximise the initial search results and also because it has previously been documented that under-reporting of ILA has previously been described.[5]

In Phase 2, qualitative information was extracted from CT reports (identified from above search criteria) and converted into structured binary data. Additional parenchymal features were screened for in CT scan reports, adjudicated and collated. Features included ground glass opacities (GGO), emphysema, traction bronchiectasis and honeycombing.[6,7] To ensure we . Specific combinations of concurrent parenchymal features (e.g. reticulation and GGO) were also collated. Importantly, traction bronchiectasis and honeycombing are considered representative of established fibrotic ILD and therefore cases with co-existing traction bronchiectasis and honeycombing identified in phase 2 were partitioned from cases of EF-ILA. Where feasible cases with reticulation and or traction bronchiectasis and or honeycombing were sub-classified into UIP categories to communicate ILA extent and co-existence to the readership.[8] This does not assume cases categorised in this manner have IPF. Similarly, cases with reticulation were subcategorised into cases with and without other non-fibrotic parenchymal abnormalities including GGO. Cases identified from the preliminary key word search (phase 1), however later found on screening (phase 2) that CT reports were detailing negative / absence of specific radiological patterns were defined as a ‘ Nil ILA’ reference cohort.

Radiographic progression was recorded as a binary event based on presence of new or increase in pre-existing parenchymal features. It was captured based upon text-based searching of CT report descriptions. Progression was adjudicated based upon perusal of all CT reports of repeat CTs by one specialist trainee (AA) using pre-defined criteria. Progression was defined as increase in either extent of identified early fibrotic features (reticulation and or GGO), new emergence of traction bronchiectasis, and/or new emergence of honeycombing on follow on CT. In cases not

demonstrating radiographic progression, this was defined as unchanged pre-existing parenchymal features and absence of new features.

Total number of subjects that underwent a thorax-protocolised CT between January-2015 and December-2020 was used as a denominator to estimate EF-ILA prevalence in cases indicated to undergo thoracic CT.

CT reporting

CT scans were assessed using text-based searching of CT reports. 80.9% of CTs were reported by 1 of 8 thoracic radiologists. All were consultants (with UK Certificate of Completion of Training/CCT for Radiology) and 7 of 8 of these consultants also held a post -CCT Thoracic Radiology Fellowship and participated in dedicated Interstitial Lung Disease MDTs. The other thoracic radiologist has >20 years of experience in reporting HRCT for ILD in our centre. The remainder were reported by one of 14 Oxford-based post CCT radiologists. Our thoracic radiologists have contributed to >20 radiology-based studies over the last decade. In one study, performed with our research group, the agreement between of reporting ILD features between the two radiologists was excellent ($r=0.91$; $p<0.001$ by Pearson's Correlation, also tested by Bland Altman; Suppl Fig 4A).[9]

Comorbidity profiles

Comorbidities for each case were search for using ICD-10 coding. Specific ICD-10 codes,[10] pertaining to respiratory and non-respiratory diagnoses were cross-referenced with electronic health records. Similarly, attendance at ILD clinic, date thereof and date of mortality obtained and time intervals between these events and CT date deduced. Comorbidities are listed as binary events. It was not possible to obtain date of comorbidity diagnoses for all cases and therefore not possible to determine which diagnoses were established prior to, at or after first CT scan showing ILA. For this reason, comorbidities were not included in all multivariate analysis and interpretation of this data is limited to association rather than causality.

Statistical analysis

Cox proportional hazard models were used to determine hazard ratios (HRs) to progression and all-cause mortality (separate models). In both models, age, gender, monocytes, neutrophils, and lymphocytes levels obtained at a time point closest to the CT scan were included. CoV values for each case were calculated from available counts for monocyte, neutrophil, and lymphocytes (and derived indexes) in the 1 year up to first CT to account for within-group variance in these measures. In separate models, CoV of longitudinal measurements for each leukocyte / index (for each subject) was included in regression models, along with the leukocyte value closest to CT. This was to adjust for any effect that variation in longitudinal measurement of these leukocyte parameters may have on clinical outcome, relative to the corresponding leukocyte value closest to CT used in the model.

Table S1

Covariate	n (%)	Death (%)	Mortality HR (95% CI)	Sig.
Age	--	--	1.01 (0.99-1.03)	0.107
Gender (Male)	1486 (54.3%)	268 (18.0%)	1.09 (0.88-1.40)	0.425
Lung cancer	269 (9.8%)	154 (57.2%)	4.98 (3.96.23)	<0.001*
Pneumonia	657 (24.0%)	251 (38.2%)	3.05 (2.45-3.81)	<0.001*
COPD / Emphysema	569 (20.8%)	165 (28.9%)	1.14 (0.90-1.43)	0.278
Nil ILA (reference)	355 (12.9%)	43 (12.1%)	--	--
Early fibrotic ILA	1259 (46.0%)	183 (14.5%)	1.52 (1.01-2.27)	0.043*
TBx without Honeycombing	490 (17.9%)	86 (17.6%)	1.70 (1.11-2.62)	0.016*
Honeycombing +/- TBx	272 (9.9%)	87 (32.0%)	3.12 (2.03-4.81)	<0.001*

Table S1 Multivariate Cox regression examining association of ILA features on first CT scan with mortality. Hazard ratios (HR) for ILA categories representative of risk relative to Nil ILA reference category. TBx; Traction bronchiectasis, EF-ILA; Early-fibrotic ILA. Model adjusted for age, gender and respiratory co-morbidity (lung cancer, pneumonia and COPD/emphysema).

Table S2

	Mortality		Radiological progression	
Covariates	HR (95% CI)	Sig.	HR (95% CI)	Sig.
-Age	1.02 (1.01-1.03)	0.015*	1.03 (1.00-1.06)	0.038*
-Gender	1.00 (0.82-1.22)	0.977	0.91 (0.66-1.26)	0.573
-Pneumonia	2.97 (2.40-3.67)	<0.001*	1.38 (0.99-1.32)	0.060
-COPD / Emphysema	1.12 (0.90-1.39)	0.294	0.64 (0.44-0.94)	0.023*
-Lung cancer	4.46 (3.61-5.51)	<0.001*	1.27 (0.80-2.00)	0.309
-Monocytes ($1x10^9$/l)	1.15 (0.85-1.55)	0.376	1.72 (1.10-2.69)	0.018*
-Neutrophils ($1x10^9$/l)	1.07 (1.04-1.10)	<0.001*	1.05 (0.98-1.12)	0.154
-Lymphocytes ($1x10^9$/l)	0.79 (0.70-0.90)	<0.001*	0.99 (0.95-1.03)	0.690

Table S2 Multivariate cox regression examining association between blood leukocyte and (i) mortality in "early fibrotic" ILA (n=1259) and (ii) radiological progression in "early fibrotic" ILA cohort with available repeat CT for comparison (n=362). Leukocytes adjusted for age, gender and respiratory comorbidities of COPD, lung cancer and pneumonia.

Table S3

Covariates	Mortality		Radiological progression	
	HR (95% CI)	Sig.	HR (95% CI)	Sig.
MLR				
-Age	1.02 (0.99-1.05)	0.059	1.02 (0.99-1.05)	0.161
-Gender	0.97 (0.71-1.33)	0.858	0.90 (0.66-1.25)	0.550
-Pneumonia	2.80 (2.02-3.87)	<0.001*	1.27 (0.91-1.79)	0.166
-COPD / Emphysema	1.31 (0.94-1.82)	0.114	0.66 (0.45-0.98)	0.038*
-Lung cancer	5.87 (4.29-8.02)	<0.001*	1.33 (0.84-2.11)	0.219
-MLR	1.21 (1.04-1.39)	0.011*	2.07 (1.19-3.62)	0.010*
NLR				
-Age	1.02 (1.01-1.05)	0.044*	1.02 (0.99-1.05)	0.160
-Gender	0.94 (0.69-1.28)	0.698	0.94 (0.68-1.29)	0.687
-Pneumonia	2.58 (1.97-3.58)	<0.001*	1.27 (0.90-1.80)	0.177
-COPD / Emphysema	1.31 (0.94-1.82)	0.113	0.69 (0.47-1.01)	0.054
-Lung cancer	6.17 (4.51-8.44)	<0.001*	1.40 (0.88-2.22)	0.153
-NLR	1.07 (1.05-1.09)	<0.001*	1.07 (1.01-1.14)	0.019*
SIRI				
-Age	1.03 (1.01-1.05)	0.034*	1.02 (1.00-1.05)	0.109
-Gender	0.98 (0.72-1.33)	0.883	0.94 (0.68-1.28)	0.676
-Pneumonia	2.75 (1.99-3.81)	<0.001*	1.33 (0.95-1.85)	0.096
-COPD / Emphysema	1.30 (0.93-1.81)	0.124	0.65 (0.44-0.96)	0.030*
-Lung cancer	5.69 (4.16-7.79)	<0.001*	1.32 (0.83-2.08)	0.241
-SIRI	1.03 (1.01-1.06)	0.007*	1.09 (1.04-1.14)	<0.001*

Table S3 Multivariate cox regression examining association between blood leukocyte indexes and (i) mortality in "early fibrotic" ILA (n=1259) and (ii) radiological progression in "early fibrotic" ILA cohort with available repeat CT for comparison (n=362). Leukocytes adjusted for age, gender and respiratory comorbidities of COPD, lung cancer and pneumonia.

Table S4

	Mortality		Radiological progression	
Covariates	**HR (95% CI)**	**Sig.**	**HR (95% CI)**	**Sig.**
Full blood count				
-Age	1.03 (1.01-1.06)	0.007*	1.03 (1.01-1.06)	0.023*
-Gender	0.96 (0.71-1.31)	0.797	0.937 (0.68-1.30)	0.700
-Monocytes ($1x10^9$/l)	1.18 (1.04-1.33)	0.011	1.74 (1.15-2.64)	0.009*
-Monocyte CoV	7.37 (3.85-14.3)	<0.0001*	7.43 (2.84-19.44)	<0.0001*
-Lymphocytes ($1x10^9$/l)	0.95 (0.84-1.07)	0.395	0.99 (0.95-1.03)	0.652
-Lymphocytes CoV	8.88 (4.72-16.4)	<0.0001*	7.50 (2.77-20.31)	<0.0001*
-Neutrophils ($1x10^9$/l)	1.08 (1.04-1.13)	<0.0001*	1.05 (0.99-1.12)	0.127
-Neutrophils CoV	4.42 (2.68-7.31)	<0.0001*	2.75 (1.28-5.90)	0.009*
MLR				
-Age	1.04 (1.01-1.06)	0.003*	1.03 (0.99-1.06)	0.065
-Gender	0.983 (0.72-1.34)	0.915	0.90 (0.65-1.24)	0.535
-MLR	1.05 (0.93-1.20)	0.441	2.03 (1.17-3.56)	0.013*
-MLR CoV	3.25 (2.42-4.37)	<0.0001*	3.08 (1.43-6.68)	0.004*
NLR				
-Age	1.04 (1.01-1.06)	0.002*	1.03 (0.99-1.06)	0.075
-Gender	0.97 (0.72-1.32)	0.859	0.95 (0.70-1.31)	0.100
-NLR	1.05 (1.03-1.07)	<0.0001*	1.08 (1.01-1.56)	0.026*
-NLR CoV	2.59 (1.83-3.59)	<0.0001*	1.41 (0.79-2.77)	0.317
SIRI				
-Age	1.04 (102-1.07)	0.001*	1.03 (0.99-1.06)	0.058
-Gender	1.04 (0.76-1.41)	0.826	0.95 (0.69-1.30)	0.731
-SIRI	1.04 (1.02-1.07)	<0.0001*	1.08 (1.03-1.14)	0.001*
-SIRI CoV	2.54 (1.93-3.37)	<0.0001*	1.62 (1.04-2.54)	0.032*

Table S4 Multivariate cox regression examining association between blood leukocyte indexes and (i) mortality in "early fibrotic" ILA (n=1259) and (ii) radiological progression in "early fibrotic" ILA cohort with available repeat CT for comparison (n=362). Covariates in “full blood count”, MLR, NLR and SIRI models adjusted for age, gender, and leukocyte co-efficient of variation (CoV).

Figure S1

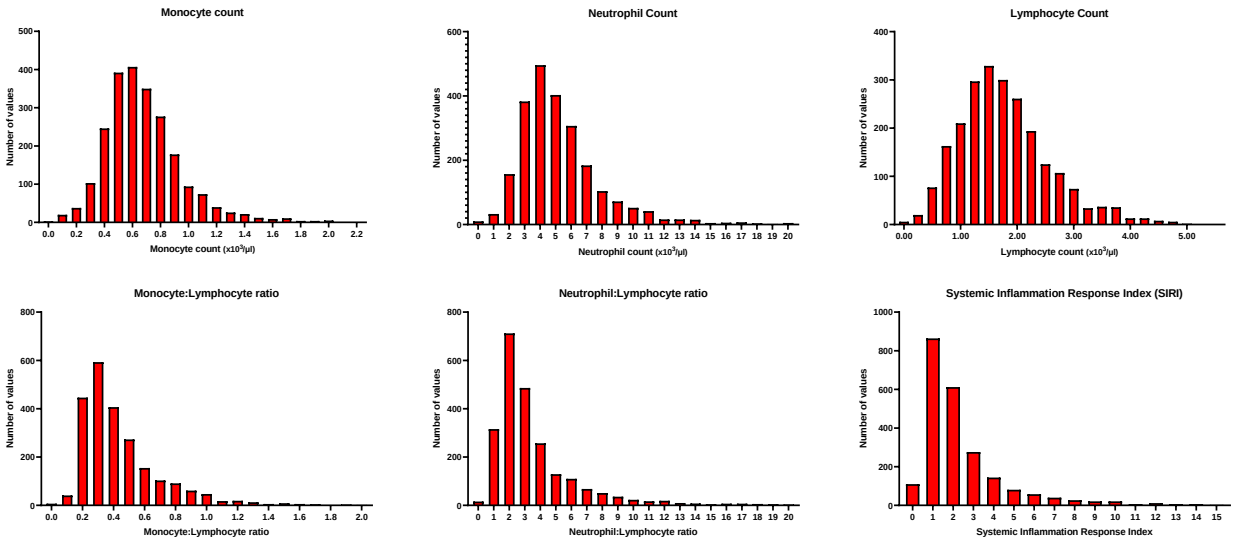


Figure S1. Histograms demonstrating Leukocyte distribution (closest value to CT)

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