EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

# Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in Fibrotic Hypersensitivity Pneumonitis: a retrospective cohort study

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Please cite this article as: De Sadeleer LJ, Hermans F, De Dycker E, *et al*. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in Fibrotic Hypersensitivity Pneumonitis: a retrospective cohort study. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.01983-2019).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

**Title: Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in Fibrotic Hypersensitivity Pneumonitis: a retrospective cohort study**

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**Main text:**

According to a survey study of Wijsenbeek and colleagues[1], 76% of respiratory physicians believe fibrotic Hypersensitivity Pneumonitis (fibrotic HP, fHP) should be treated with corticosteroids (CS) as first line treatment. However, data to support such a strategy are limited and confined to acute farmer's lung[2]. Classically, HP patients are classified according to symptom chronicity in acute and chronic HP[3]. Based on new data, however, a stratification according to the (radiological) presence of fibrosis seems more in line with prognosis[4]. In an earlier study[5], we demonstrated that CS treatment was only beneficial in non-fibrotic HP (nfHP) while CS was not effective in fHP, both in terms of survival, FVC% decline and DLCO% decline. In this study, we determined whether the presence of broncho-alveolar lavage lymphocytosis (BAL Lymphocytosis, BALL) or honeycombing (HC) influences the treatment effect of CS in fHP patients.

We included all fHP patients followed in the University Hospitals Leuven between 2005 and 2016. Patients without BAL were excluded. Validation of HP diagnosis was performed using symptoms, CT findings and pathological findings as described previously[5]. As only fibrotic patients were included, CT scans were reviewed for the presence of extensive reticulation, traction bronchiectasis or honeycombing (as defined by the Fleischner Society[6]). BALL was dichotomized as 'high' when >20% and 'low' when ≤20%. We analyzed the survival effect of both BALL and HC presence using a cox proportional hazards model corrected for age, gender and baseline FVC%. The effect of corticosteroid treatment on pulmonary function (PFT) was analyzed using mixed models comparing FVC% and DLCO% trajectories before treatment initiation with post-treatment FVC% and DLCO% trajectories. CS use was included both with and without time-dependent covariate. Age, gender, active exposure and use of second line immunosuppressive treatment (the latter as time-dependent covariate) were included as fixed effect. Subject and the PFT test-performing hospital were included as random effects (the former as random intercept and independent random slope, the latter as

random intercept). PFT tests were included from 5 years before treatment initiation until 1 year after initiation or until treatment interruption.

91 fHP patients were included in the study. Mean age was 64.6 (±11.9), 32 patients (35.2%) were female. Baseline FVC% and DLCO% were 73.6% (±21.7%) and 46.7 (±17.8%) respectively. 67 patients (73.6%) were treated with corticosteroids, 20 patients (21.9%) received concomitant 2$^{nd}$ line immunosuppressive drugs; 36 patients (40%) had high BALL, 55 had low BALL (60%); 58 patients (64%) had no HC, 33 patients (36%) had HC. Low BALL was associated with increased HC presence (low vs high BALL: 50.9% vs 13.9%, p<0.001). No other differences in baseline characteristics were noted between low and high BALL patients. HC presence was associated with decreased BAL lymphocytosis (HC present vs absent: 11.8% vs 24.1%, p=0.002) and lower DLCO% (40.7% vs 49.8%, p=0.025). No other differences in baseline characteristics were noted between patients with and without HC. Exposure type (mold vs birds vs other vs unknown exposure) was not associated with BALL (p=0.37), HC presence (p=0.21) or death (p=0.2).

Both low BALL and HC presence were associated with poor 10-year survival (low BALL: HR 2.66, CI 1.05-6.73, p=0.038; HC presence: HR 3.80, CI 1.66-8.73, p=0.002) as depicted in Figure 1A and 1B. In a cox proportional hazards model including both BALL and HC presence (corrected for age, gender and baseline FVC%), only HC was associated with poor outcome (HC: HR 2.68, CI 1.02-7.06, p=0.046; BALL: HR 1.4, CI 0.51-4.09, p=0.49). Patients with high BALL experienced an FVC% increase of 5.66% (p=0.004) after CS initiation, although FVC% decline (i.e. the slope of the mixed model) was similar (-6.6%/year before vs -5.3%/year after CS initiation, p=0.77). No effect on DLCO was observed (main effect (i.e. the intercept): p=0.29, decline (i.e. slope of the model): p=0.50). No CS effect was seen in the low-BALL group (FVC% main effect: p=0.93; FVC% decline: p=0.96; DLCO% main effect: p=0.50; DLCO% decline: p=0.33). Patients without HC experienced a trend towards FVC% increase of 4.21% (p=0.07) after CS initiation, although FVC% decline was not affected (-1.4 %/year before vs -2.82%/year after CS initiation, p=0.78). No effect on DLCO was observed (main effect: p=0.12,

decline: p=0.91). No CS effect was seen in the group with HC (FVC% main effect: p=0.80; FVC% decline: p=0.57; DLCO% main effect: p=0.33; DLCO% decline: p=0.24). Pulmonary function trajectories are depicted in Figure 1C and 1D.

While CS initiation had a marginal effect on FVC when BALL was high and when HC was absent, no effect was seen when BALL was low or when HC was present. However, this single center retrospective study has some limitations. As BAL lymphocytosis and HC were correlated in this cohort of 91 patients, there was a lack of statistical power to assess the differential contribution of both variables on FVC increase after treatment initiation. Hence, it is unclear whether the increase of FVC in patients without HC is attributable to the absence of HC or the associated presence of high BALL. Larger multicenter trials are needed to address this question.

As no generally accepted cut-off for high BAL Lymphocytosis exists, we opted for the cut-off used in our ILD clinic (i.e. 20%). Moreover, analysis of c-indices showed a 20% cut-off yielded the best prognostic separation (c-index = 0.635); better compared to a 25% cut-off (c-index 0.59, p=0.029), a 30% cut-off (c-index 0.60, p=0.084) and a 40% cut-off (c-index 0.51).

We strongly believe that the risks of initiating CS therapy should be balanced against the marginal gains in the subgroup with high BALL/no HC. The recently published Nintedanib trial in progressive fibrosing ILDs (PF-ILDs)[7] complicates the decision to initiate CS in fHP patients with high BALL or absence of HC even more. In order to assess whether fHP patients are progressive (which would indicate antifibrotics are warranted), a careful observation of FVC% decline of at least 5% is warranted, based on the Nintedanib trial[7]. The marginal increase in FVC% after CS initiation would postpone the moment reaching a 5% decline in FVC% since diagnosis (while CS does not alter the progressive nature of the disease itself), merely delaying the start of antifibrotic treatment.

As the gains of CS initiation in high BALL fHP patients and/or patients without HC are expected in the early stage of treatment and side-effects become more frequent as treatment duration increases,

we believe these data do not support a long-term corticosteroid treatment. However, multi-center randomized controlled trials are needed to assess this question.

In conclusion, both low BAL lymphocytosis and HC presence predict poor outcome and absence of CS treatment effect. In fHP patients with high BALL or HC absence, a marginal increase in FVC was seen, although FVC decline nor DLCO decline changed after CS treatment initiation.

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## Author Contributions

Study design: LJDS and WAW; data retrieval: LJDS, EDD and FH; data analysis: LJDS; manuscript writing: LJDS, SV and WAW; reviewing and editing: all authors.


## Funding

Research reported in this publication was supported by the Research Foundation—Flanders and the University Hospitals Leuven (1.8.325.12N). The funding sources were not involved in study design, data collection, data analysis, data interpretation, manuscript writing or the decision to submit the article for publication.

## Acknowledgments

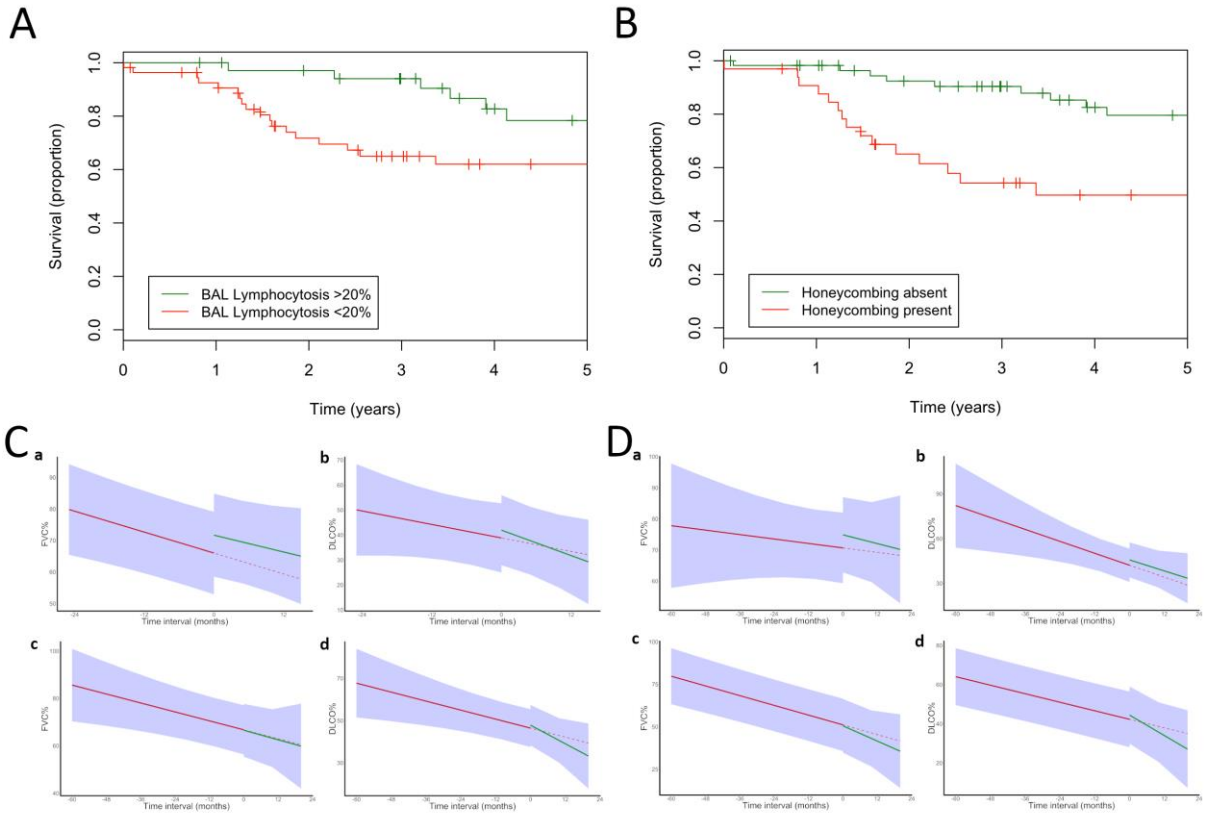
We thank the patients who participated in this study.


## Conflicts of Interest

Dr De Sadeleer reports non-financial support from Roche and Boehringer-Ingelheim, outside the submitted work. Prof Dr. Wuyts reports grants from Roche, grants from Boehringer-Ingelheim, grants from fund scientific research Flanders, grants from National institute of Health, all payed to the institution (University Hospitals Leuven), outside the submitted work. Dr Hermans, Mrs De Dycker, Prof Dr Yserbyt, Prof Dr Verschakelen, Prof Dr Verbeken, and Prof Dr Verleden have nothing to disclose.

**Figure 1: Impact of BALL and HC in fHP.**

(A) Impact of BALL on survival (B) impact of HC on survival (C-D) Impact of BALL (C) and HC (D) on pulmonary function test trajectories. The solid red line represents the pre-treatment trajectory, the green line represents the post-treatment trajectory, the dotted red line represents the pretreatment-trend. (Ca) FVC% trajectory in high BALL patients, (Cb) DLCO% trajectory in high BALL patients, (Cc) FVC% trajectory in low BALL patients, (Cd) DLCO% trajectory in low BALL patients, (Da) FVC% trajectory in patients without HC, (Db) DLCO% trajectory in patients without HC (Dc), FVC% trajectory in patients with HC, (Dd) DLCO% trajectory in patients with HC.


A
Survival (proportion)
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Time (years)
BAL Lymphocytosis >20%
BAL Lymphocytosis <20%
B
Survival (proportion)
Time (years)
Honeycombing absent
Honeycombing present
C
a
b
c
d
FVC%
DLCO%
Time interval (months)
D
a
b
c
d
FVC%
DLCO%
Time interval (months)