# Disease Relapse Rate from Long-Term Follow-Up Data in Löfgren's Syndrome

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*To the Editor*:

Sarcoidosis is a systemic inflammatory disorder of unknown cause, characterized by the formation of noncaseating epithelioid cell granulomas and a heterogeneous clinical course (1). A well-defined phenotype of sarcoidosis is Löfgren's syndrome (LS), which manifests as acute onset, bilateral hilar lymphadenopathy, erythema nodosum, and/or bilateral ankle arthritis or periarticular inflammation (2). LS is most commonly seen in North and Western Europe and is strongly associated with the presence of *HLA-DRB1*03* (3). Patients with LS usually have a very good prognosis; up to 95% of patients who are *HLA-DRB1*03* positive (+) experience resolving disease within 2 years (4). In contrast, *HLA-DRB1*03* negative (−) patients have a less favorable disease course, with only 51% of patients experiencing resolving disease within 2 years. Furthermore, the presence of *HLA-DRB1*15* is a risk factor for nonresolving disease in LS (4).

In patients with LS with resolving disease, a relapse rate of 3–8% (4, 5) was found in a follow-up period of up to 5 years; however, no long-term follow-up data are available. The aim of the current study was to determine the long-term relapse rate in a large cohort of Dutch patients with LS. Furthermore, *HLA-DRB1*03* and *HLA-DRB1*15* were determined, to investigate a possible association with long-term outcome.

From 1959 to 2020, 380 patients were diagnosed with LS in our hospital. These 380 patients were invited for a reevaluation, which 207 patients (54%) accepted; they underwent clinical evaluation, laboratory tests, lung function test, and chest X-ray. Medical records were reviewed for clinical data. Patients were classified as having resolving disease when there were no signs of disease 2 years after onset and as having nonresolving disease when there were signs of ongoing disease 2 years after onset. Tag SNPs rs2040410A and rs3135388A were used to capture *HLA-DRB1*03* and *HLA-DRB1*15*, respectively, as previously described (6). A descriptive analysis was performed expressing the results as median and interquartile range (IQR) for continuous variables and absolute values and percentages for categorical variables. A Mann-Whitney *U* test was performed for the comparison between continuous variables and the chi-square test for the comparison of categorical variables.

Baseline characteristics are presented in Table 1, showing that the majority of the patients with LS were *HLA-DRB1*03*+ (71%) and female (60%). Within 2 years after presentation, 94% of patients with LS demonstrated a spontaneous resolution of disease, with a higher percentage of resolution in the *HLA-DRB1*03*+ patients compared with *HLA-DRB1*03*− patients (100% vs. 74%, respectively; $P < 0.00001$). Nonresolving disease only occurred in 10 patients, who were all negative for *HLA-DRB1*03* and of whom 5 were *HLA-DRB1*15*+.

During the long-term follow-up period (median, 10.8 yr; IQR, 4.3–20.6 yr), 11% of the cohort experienced relapsing disease after a median period of 5.5 years (IQR, 3.0–10.5 yr; Figures 1A and 1B), with 50% of the patients relapsing more than 5 years after the initial diagnosis.

Interestingly, in the group of *HLA-DRB1*03*+ patients who experienced a relapse, only 38% relapsed as LS, whereas this was 89% in the *HLA-DRB1*03*− patients ($P = 0.03$). Furthermore, significantly more relapsing *HLA-DRB1*03*− patients were *HLA-DRB1*15*+ compared with relapsing *HLA-DRB1*03*+ patients ($P = 0.004$). *HLA-DRB1*03*− patients who developed chronic disease after a relapse were also more often positive for *HLA-DRB1*15*. Positivity for *HLA-DRB1*15* was significantly associated with the form of relapsing disease and was significantly more common in patients developing chronic disease after relapse.

For 132 patients, we have complete data of treatment and resolving and relapsing disease. Of these patients, 32% received oral steroid treatment upon diagnosis. There was no significant difference in treatment between *HLA-DRB1*03*+ and *HLA-DRB1*03*− patients. In patients treated with steroids, significantly more *HLA-DRB1*03*− patients had nonresolving disease, as expected, because all *HLA-DRB1*03*+ patients had resolving disease (Table 1). Interestingly, among the *HLA-DRB1*03*− patients treated with oral steroids, 7 out of 13 (54%) had a resolving disease course, whereas among the nontreated *HLA-DRB1*03*− patients, 17 out of 19 (89%) had resolving disease ($P = 0.022$) (Figure 2). No difference was found in the proportion of treated and nontreated relapsing patients.

Data on long-term follow-up are scarce in patients with LS. Previously, Grunewald and Eklund (4) described a large cohort of patients with LS with a follow-up period of at least 2 years, without describing the maximum follow-up period. They found that only 1% of *HLA-DRB1*03*+ patients had nonresolving disease and 4% had relapsing disease, whereas 49% of the *HLA-DRB1*03*− patients had nonresolving disease and none had relapsing disease. The percentage of *HLA-DRB1*03*+ in our patients with LS was similar, but relapsing disease in our *HLA-DRB1*03*+ patients was much higher (9%) after a median period of 7.0 years (IQR, 3.5–16.0 yr) of follow-up. As depicted in Figures 1A and 1B, our data suggest that relapse may occur at any point in time during follow-up and that patients remain at increased risk for sarcoidosis for at least 10 years after diagnosis.

Furthermore, in comparison with patients from Sweden described by Grunewald and Eklund (4), particularly *HLA-DRB1*03*− patients showed more often (74% vs. 51% in Sweden) resolving disease and a much higher frequency (16% vs. 0% in Sweden) of relapsing disease. In line with this, in our cohort, fewer *HLA-DRB1*03*− patients treated with oral steroids showed nonresolving disease compared with the Swedish cohort (46% vs. 80%, respectively). Although this suggests that treatment may be a beneficial option in some patients, our number of treated *HLA-DRB1*03*− patients is low and stems mainly from the period before 1990.

Supported by ZonMw grant 842002001.

Originally Published in Press as DOI: 10.1164/rccm.202307-1291LE on January 29, 2024

**Table 1.** Baseline Characteristics and Disease Course in Subjects Ever Diagnosed with LS

| | All Patients | *DRB1*03+* | *DRB1*03−* | *P* Value |
|---|---|---|---|---|
| Demographics | 207 | 146 (71) | 61 (29) | |
| Year of diagnosis | | | | |
| 1959–1990 | 48 (23) | 32 (22) | 16 (26) | |
| 1991–2000 | 60 (29) | 51 (35) | 9 (15) | |
| 2001–2010 | 57 (28) | 36 (25) | 21 (34) | |
| 2011–2020 | 42 (20) | 27 (18) | 15 (25) | |
| Median age at diagnosis, yr (IQR) | 34.4 (20.8–67.9) | 34.4 (20.8–64.1) | 34.5 (20.8–67.9) | 0.96 |
| Sex, m/f | 83/124 (40/60) | 63/83 (43/57) | 20/41 (33/67) | 0.17 |
| Smoking history | 198 | 142 (72) | 56 (28) | |
| Current smoker | 43 (22) | 35 (24) | 8 (14) | 0.13 |
| Ex-smoker | 55 (28) | 42 (30) | 13 (23) | 0.48 |
| Never-smoker | 100 (51) | 65 (46) | 35 (63) | 0.04 |
| Fever ($n=165$) | 99 (60) | 78 (64) | 21 (49) | 0.08 |
| EN ($n=201$) | 162 (81) | 117 (81) | 45 (79) | 0.71 |
| Periarticular ankle arthritis ($n=199$) | 151 (76) | 109 (77) | 42 (72) | 0.46 |
| Both EN and ankle arthritis ($n=196$) | 110 (56) | 82 (59) | 28 (50) | 0.28 |
| *HLA-DRB1*15+* | 42 (20) | 17 (12) | 25 (41) | $P<0.00001$ |
| Disease course >2 yr available | $n=153$ | $n=114$ | $n=39$ | |
| Resolving disease | 143 (93) | 114 (100) | 29 (74) | $P<0.00001$ |
| Nonresolving disease | 10 (7) | 0 | 10 (26) | $P<0.00001$ |
| Nonresolving disease, *HLA-DRB1*15+* | | | 5 (50) | |
| Long-term follow-up available | $n=201$ | $n=144$ | $n=57$ | |
| Median follow-up, yr (IQR) | 10.8 (4.3–20.6) | 11.4 (3.8–20.6) | 9.4 (5.6–20.7) | 0.64 |
| Relapsing disease | 22 (11) | 13 (9) | 9 (16) | 0.18 |
| Relapsing disease, *HLA-DRB1*15+* | 7 (32) | 1 (8) | 6 (67) | <0.004 |
| Median time to relapse, yr (IQR) | 5.5 (3.0–10.5) | 7.0 (3.5–16.0) | 4.0 (3.0–6.5) | 0.39 |
| Relapse as LS | 13 (59) | 5 (38) | 8 (89) | 0.018 |
| Relapse as LS, *HLA-DRB1*15+* | 5 (38) | 0 | 5 (63) | 0.024 |
| Chronic after relapse | 11 (50) | 5 (38) | 6 (67) | 0.19 |
| Chronic after relapse, *HLA-DRB1*15+* | 6 (55) | 1 (20) | 5 (83) | 0.036 |
| Data treatment available* | $n=132$ | $n=100$ | $n=32$ | |
| Treated | 42 (32) | 29 (29) | 13 (41) | 0.219 |
| Nonresolving disease | 6 (14) | 0 | 6 (46) | $P<0.0001$ |
| Relapsing disease | 7 (17) | 5 (17) | 2 (15) | 0.881 |

*Definition of abbreviations*: EN = Erythema nodosum; LS = Löfgren's syndrome.
Data are presented as *n* (%) unless otherwise noted. *P* value for comparison between *HLA-DRB1*03* positive (+) and negative (−) patients.
*Treatment with oral steroids upon diagnosis.

Of our relapsing *HLA-DRB1*03−* patients, 67% carried the *HLA-DRB1*15* allele, which makes it even more remarkable that we found that more *HLA-DRB1*03−* patients had clinical signs of LS during relapsing compared with *HLA-DR1*03+* patients. Because of the strong association between *HLA-DR1*03+* and LS, one would expect the opposite.

The strength of the study involves the high number of patients with clinical reevaluation and long-term follow-up data. However,

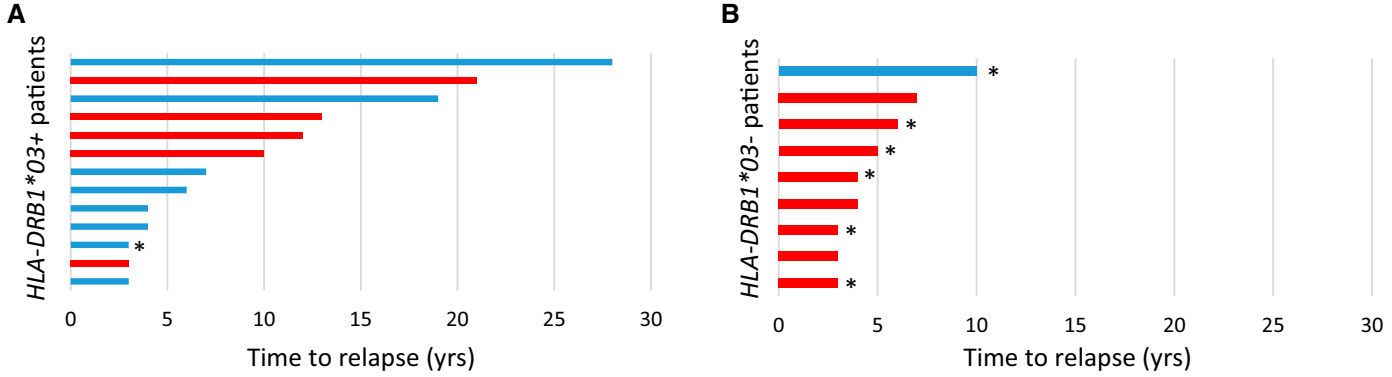


**Figure 1.** (*A* and *B*) Time to relapse after initial diagnosis of Löfgren's syndrome (LS) and form of relapsing disease for each relapsing *HLA-DRB1*03+* patient (*A*) and relapsing *HLA-DRB1*03−* patient (*B*). Relapse is shown as LS (red) or sarcoidosis (blue). **HLA-DRB1*15+*.

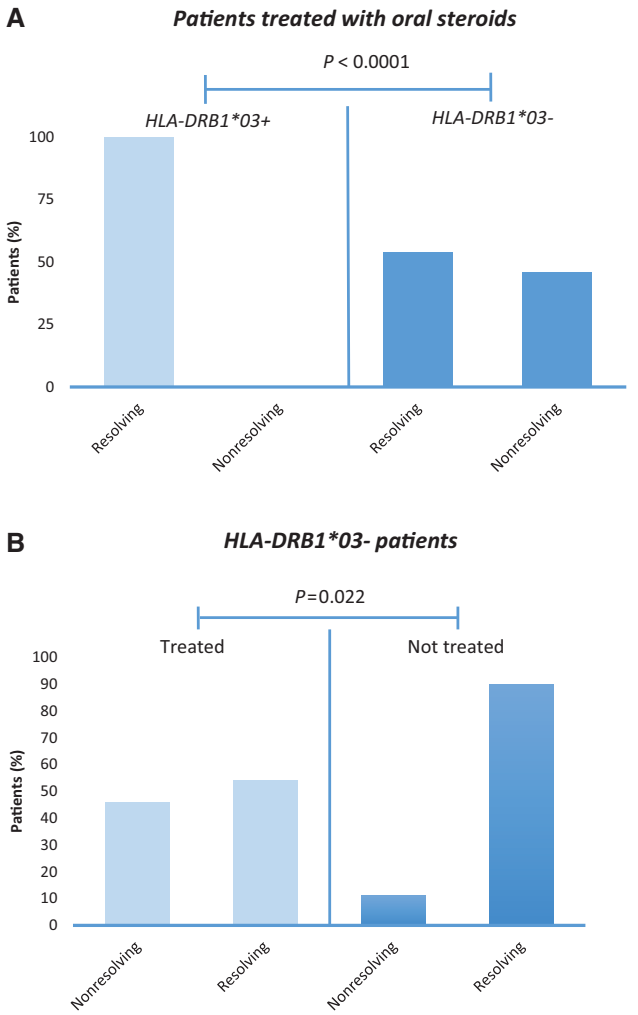


**Figure 2.** (*A*) Disease course of *HLA-DRB1*03+* and *HLA-DRB1*03−* patients, showing the relative numbers for resolving and nonresolving disease. (*B*) Disease course in *HLA-DRB1*03−* patients treated ($n = 13$) or not treated ($n = 19$) with oral steroids.

this study has its limitations, as only 54% of invited patients participated, which may have caused inclusion bias toward relapsing and nonresolving disease. Therefore, it could be that the prevalence of nonresolving disease or relapse in Dutch patients with LS is lower than reported in our study. Furthermore, all associations are unadjusted.

To conclude, this is the first study describing long-term follow-up in LS. In our cohort of Dutch patients with LS, we found a relapse rate as high as 11%, with 50% of relapses occurring more than 5 years after the initial diagnosis. Furthermore, our data suggest that the type of *HLA-DRB1* influences not only the evolution toward resolving disease but also the risk of relapse and even the accompanying clinical phenotype at the time of relapse. *HLA-DRB1* tagging (6), which is simple and inexpensive to perform, could be used in clinical practice to inform patients with LS about both their short- and long-term prognoses. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Unadjusted Lower Limit of Normal for Airflow Obstruction

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*To the Editor*:

Airflow obstruction is defined by a low ratio of $FEV_1$ to FVC. However, the best threshold to use for defining a low versus a normal

Supported by NIH grants R01 HL151421, UH3HL155806, K01HL163249, R21HL153700, K23HL130627, R21HL129924, and R21HL121457.

Author Contributions: Study concept and design: S.P.B. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: S.P.B. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: S.P.B. Study supervision: all authors.

Originally Published in Press as DOI: 10.1164/rccm.202312-2301LE on February 1, 2024