

1 **Predictors of access to care in Juvenile Systemic Lupus Erythematosus**
2 **(JSLE) – Evidence from the UK JSLE Cohort Study**

3

4 **Short title:** Access to care in JSLE

5

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25 diagnosis, access to care, cohort

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34 List of non-standard abbreviations: JSLE = Juvenile Systemic Lupus
35 Erythematosus, ACR = American College of Rheumatology, JIA = Juvenile
36 Idiopathic Arthritis, RA = Rheumatoid Arthritis, SLE = Systemic Lupus
37 Erythematosus, IQR = interquartile range, NHS = national health service.

38

39 **Abstract (250 words):**

40

41 **Background:** Timely access to comprehensive specialist care is crucial in
42 Juvenile Systemic Lupus Erythematosus (JSLE) with barriers in access to
43 specialist care having the potential to negatively influence disease trajectory
44 and outcomes. **Objectives:** To investigate factors that may influence the
45 interval between symptom-onset and JSLE diagnosis. **Methods:** Data from all
46 patients recruited to the UK JSLE Cohort Study between 2006-2011 and
47 meeting American College of Rheumatology (ACR) criteria for lupus were
48 analysed. Variables associated with time between symptom-onset and
49 diagnosis were identified using correlation tests. Linear regression was used
50 to identify independent predictors of access to care. **Results:** Two hundred
51 and fifty seven children with JSLE were included in the analysis (216 females,
52 41 males, ratio 5.3:1). Median time from symptom-onset to diagnosis was 0.4
53 years (range 0.0-14.1 years, inter-quartile range [IQR] 0.2-1.4). A linear
54 regression model identified being of African or Caribbean origin ($p=0.006$),
55 Asian ($p=0.045$), referred by a paediatrician ($p=0.047$) or having nephritis
56 ($p=0.045$) at presentation, as independent predictors of shorter time to
57 diagnosis. Being of Caribbean or Asian origin, compared to white, was
58 associated with a 56% and 37% reduction in geometric mean time to
59 diagnosis respectively. Similarly, being referred to paediatric rheumatology by
60 a paediatrician or having nephritis at presentation, was also associated with a
61 32% and 36% reduction in geometric mean time to diagnosis respectively.
62 **Conclusion:** Within this national UK cohort, ethnic origin, initial source of
63 referral and having lupus nephritis at presentation, were strong predictors of

64 the interval to establishing a diagnosis of JSLE.

65

66 **Background:**

67

68 Delays in diagnosis and initial access to specialist care are well reported in

69 Juvenile Idiopathic Arthritis (JIA), Rheumatoid Arthritis (RA) [1, 2] and have

70 been reported in Juvenile-onset Systemic Lupus Erythematosus (JSLE) [3].

71 Diagnosis in JSLE can be challenging as the condition often presents with

72 non-specific symptoms, such as fatigue, arthralgia, mouth ulcers and

73 headaches, occurring intermittently and cumulatively over many months.

74 Conversely, presentation can be acute with potentially life-threatening

75 manifestations e.g. renal failure or seizures. Major organ involvement is more

76 prevalent in JSLE than in adult-onset SLE with more rapid accrual of disease

77 related damage [3-5]. There is no single diagnostic test and diagnosis relies

78 upon awareness and experience, comprehensive clinical assessment,

79 judicious interpretation of investigations and often exclusion of other

80 conditions such as malignancy.

81

82 In both RA and JIA, reducing the time from diagnosis to starting disease

83 modifying anti-rheumatic drugs is important in optimising outcomes [6, 7].

84 Otten et al recently investigated the relationship between disease activity

85 patterns and early aggressive treatment in JSLE. Patients who were treated

86 aggressively at an early stage (within 6 months) subsequently had a more

87 favorable disease course (longer quiescence pattern), compared to patients

88 who were not treated aggressively early (chronically active disease pattern)

89 [8].

90

91 There is a marked paucity of previous studies exploring access to specialist
92 care in JSLE when compared to JIA, RA and SLE [2, 6, 7, 9, 10]. The Euro-
93 Lupus cohort, including 1000 patients (76 with JSLE) from 7 European
94 countries has reported a mean time from initial symptom onset to diagnosis of
95 2 and 5 years in adult-onset and JSLE, respectively. The authors concluded
96 that 'doctors were reluctant to diagnose SLE in children because typical signs
97 and symptoms are less common and the milder manifestations of SLE may be
98 missed in a paediatric population' [3].

99

100 The UK JSLE Cohort Study was established in 2006 by the UK JSLE Study
101 Group (<http://www.liv.ac.uk/ukjsle>), with the aim of documenting a prospective
102 cohort of JSLE patients. It collects detailed information on demographics,
103 ACR SLE criteria [11], disease activity, medication use and disease damage
104 indices. The aim of the present study was to investigate factors that may
105 influence the interval between symptom-onset and JSLE diagnosis, using
106 data collected by the UK JSLE Cohort study over 5 years.

107

108 **Patients and methods:**

109

110 The general characteristics of the UK JSLE Cohort Study have recently been
111 described [12]. In brief, the study is organised from a national coordinating
112 centre in Liverpool and includes children and young people with onset of

113 JSLE prior to the age of 17 years. Patients are recruited to the cohort from all
114 major paediatric rheumatology and nephrology centres across the UK.

115

116 Written parental consent / patient consent or assent to take part in the study
117 was obtained from all patients and families involved in accordance with the
118 declaration of Helsinki. The study has received ethical approval from the
119 North West National Research Ethics Service Committee, Liverpool East, and
120 is supported by the UK Clinical Research Network Study Portfolio (for details,
121 see <http://public.ukcrn.org.uk/search/>). Patients were eligible for the current
122 study if they were recruited to the UK JSLE cohort between 2006-11 and met
123 four of the eleven established ACR criteria for lupus [11].

124

125 Bespoke *a priori* case report forms collect comprehensive clinical and
126 demographic data for each JSLE patient. From clinical experience and
127 previous studies [2, 7, 10, 11] we investigated a number of variables
128 considered of potential relevance to accessing specialist care. These
129 included, demographic factors (ethnicity, gender, age at presentation,
130 socioeconomic status, family history of autoimmune disease including SLE,
131 rheumatoid arthritis, thyroid abnormalities, connective tissue disease, type 1
132 diabetes in a first degree family relative), factors associated with disease
133 severity (presenting features, ACR SLE criteria) and mode of referral (origin of
134 referral to paediatric rheumatology, distance from nearest tertiary paediatric
135 rheumatology service). Self reported patient ethnicity was defined according
136 to the UK National Census categorisations [13]. The data of patients who
137 were of mixed race were grouped with those of the associated ethnic minority

138 group (e.g. Asian and Asian / Mixed ethnic origin patient data combined
139 during analysis). The English index of multiple deprivation for 2007 (derived
140 from postcodes) was used as a measure of small area deprivation of area of
141 residence [14].

142

143 Time from symptom onset to diagnosis was non-normally distributed with a
144 long tail of higher values. Therefore, the data were log transformed to give a
145 broadly normal distribution. Variables correlated with the log of time between
146 symptom-onset and diagnosis were identified ($p < 0.1$). Linear regression was
147 then used to identify independent predictors of access to care ($p < 0.05$).
148 Wilcoxon rank-sum test was used to compare the IMD scores of the Cohort
149 population in 2007, with that of the English population in 2007 as a whole.
150 Data were expressed as percentages, median, range and interquartile ranges
151 (IQR). Results were analysed using SPSS version 19 software (SPSS,
152 Chicago, IL, USA).

153

154 **Results:**

155 A total of 257 participants were eligible and their demographic data are
156 presented in Table 1. The cohort comprised a preponderance of females and
157 wide range of ethnic diversity. The median time from symptom onset to
158 diagnosis is 0.4 years (range 0.0-14.1 years, IQR 0.2-1.4 years). 143/258
159 patients (55%) were diagnosed within 6 months of symptom onset and a
160 further 32/258 patients (12%) were diagnosed within 12 months. Referrals to
161 paediatric rheumatology directly from primary care were uncommon (11%)
162 with the remainder of referrals being from general paediatrics and sub-

163 specialists. A family history of autoimmune disease in a first-degree family
164 relative was present in 27% of patients. The median distance from the
165 patient's home to a tertiary paediatric rheumatology centre was 21.3 miles
166 (range 0.1-154.9, IQR 9.5-48.6 miles). The JSLE cohort population Index of
167 Multiple Deprivation scores were found to be higher than the English
168 population as a whole ($p < 0.001$).

169

170 Variables correlating with log of time to diagnosis, and identified as
171 independent predictors of shorter time to diagnosis are shown in Table 2.
172 Being Caribbean or Asian, compared to white, was associated with a 56%
173 and 37% reduction in geometric mean time to diagnosis respectively. Being
174 referred to a paediatric rheumatology service by a paediatrician and having
175 nephritis at presentation, was also associated with a 32% and 36% reduction
176 in geometric mean time to diagnosis respectively. Gender, age at
177 presentation, ACR score, distance from nearest tertiary paediatric
178 rheumatology service, socioeconomic status and family history of autoimmune
179 disease were not found to be significant predictors of access to care.

180

181 **Discussion:**

182

183 We undertook an observational study of a UK JSLE cohort and demonstrated
184 that ethnic origin, initial source of referral and having lupus nephritis at
185 presentation were strong predictors of reduced interval to establishing a
186 diagnosis. In contrast to what might have been anticipated from clinical
187 practice and previous studies [2, 3, 5, 10], gender, age at presentation, ACR

188 score, distance from nearest tertiary paediatric rheumatology service,
189 socioeconomic status and family history of autoimmune disease were not
190 found to be significant predictors of access to care.

191

192 The baseline demographic and clinical data from this large, national,
193 multicentre collaborative UK JSLE Cohort Study highlight the considerable
194 variation in time taken to achieve a diagnosis of JSLE within the UK, with
195 some patients being diagnosed quickly, and others facing major delays.
196 These data suggest that multiple referrals occur within secondary and tertiary
197 care before accessing paediatric rheumatology care, providing important
198 insights into potential factors that may contribute to the wide variation in time
199 taken to achieve a diagnosis. The importance of early diagnosis is highlighted
200 by clinical outcome data for lupus nephritis [15], and also by the observation
201 that patients with JSLE from the US who lack comprehensive medical
202 insurance and have reduced access to care, have higher rates of
203 complications [10].

204

205 Previous studies exploring access to care in JIA suggest that the explanation
206 for delay in referral is multi-factorial, with the experience and knowledge of the
207 healthcare professionals to whom the family present being paramount, as well
208 as social, cultural, organisational and health network related factors [2, 3, 16].
209 General practitioners and paediatric trainees have been shown to display poor
210 confidence in paediatric musculoskeletal assessment [17] and a lack of
211 awareness of rheumatic diseases in children and young people. In response
212 to this, innovative educational resources have been developed to improve

213 paediatric musculoskeletal examination skills [18]. Adaptation of existing
214 resources or development of JSLE specific resources is required, as the
215 increased incidence of internal organ involvement in JSLE may negatively
216 influence the 'visibility' of disease [12, 19].

217

218 In adult SLE it is known that socio-demographic disparities exist in relation to
219 both initial and on-going access to healthcare, resulting in differences in long-
220 term outcomes, hospitalisations, morbidity and ultimately mortality [10]. These
221 observations have mainly come from American studies, and emphasise the
222 contribution of ethnicity, gender, education, adherence, social support,
223 socioeconomic status, mode of healthcare delivery, medical insurance type
224 and geographical location of appropriate healthcare, as determinants of
225 access to care. The relative influence of individual factors is difficult to
226 disentangle, as many social determinants of health frequently co-exist.

227

228 Specific factors such as distance to a paediatric rheumatology centre may be
229 more of an issue in a large county like the US, and determinants of access to
230 care may also differ according to the populations' basic demographics and
231 healthcare system structure. In terms of access to and use of care in chronic
232 diseases, the literature suggests a different picture in adults and children,
233 whereby care tends to be more equitably delivered to children [20]. In the UK
234 National Health System (NHS), where care is universally free at the point of
235 access, some studies have suggested equality of access to secondary care
236 services in children by socioeconomic status [21], whereas others have
237 demonstrated inequity in the utilisation of specialist services in relation to

238 socio-economic status (e.g. in eye-care services) [22]. A further study of cystic
239 fibrosis care suggested that UK clinicians consider deprivation status as well
240 as diseases status when making decisions about treatments, potentially
241 mitigating some of the effects of social disadvantage on health outcomes [23].

242

243 A qualitative study looking at the perceptions of healthcare provision in adults
244 with SLE in the UK has described four main themes which relate to patient
245 experiences; *'searching for an answer'*, *'nobody can understand'*, *'are they*
246 *really listening'* and *'joining the dots'*. These themes highlight the diagnostic
247 difficulties faced by adults with SLE, the lack of basic understanding of SLE by
248 GP's and healthcare providers, and the need for cohesive healthcare [24].

249 These experiences may resonate with those of young people with JSLE, but
250 in view of the known significant differences between childhood and adult
251 onset SLE [3-5, 12], it is likely that additional and distinct factors may be of
252 importance.

253

254 Strengths of this study include the large, nationally representative,
255 prospectively collected data, however, the limitations must be acknowledged.

256 The UK JSLE Cohort Study was not specifically designed to explore barriers
257 and drivers of access to care, and does not collect detailed data on the time-
258 period prior to diagnosis. Clearly there is a potential bias towards patients
259 seen at large tertiary centres connected to the UK JSLE Cohort study, with
260 data lacking from patients who have been managed in other paediatric
261 centres or in adult healthcare. The number of patients described is smaller
262 than in some adult lupus cohorts [10], and consequently the study may not be

263 adequately powered to detect the influence of all previously described
264 determinants of access to care. Other potentially important covariates such as
265 age, occupation, level of educational attainment, marital status, social support
266 of parents / carers and existing knowledge of JSLE are currently not collected
267 by the UK JSLE cohort study, but may also bear influence on access to care.
268 Our study provides insight and a basis on which to design further studies to
269 gain a more in-depth understanding of the barriers and facilitators to
270 appropriate care and achieving a diagnosis in JSLE.

271

272 In conclusion, timely access to comprehensive specialist care is crucial in
273 JSLE. The UK JSLE Cohort Study data demonstrates that there is
274 considerable variation in time taken to achieve a diagnosis of JSLE within the
275 UK. Future studies combining qualitative and quantitative methodologies are
276 warranted to provide important insights into the experiences and challenges of
277 achieving a diagnosis of JSLE. Recognition of such barriers and facilitators to
278 appropriate care will inform recommendations for interventions and strategies
279 to improve access to and delivery of specialist care in JSLE across the
280 boundaries of paediatric, adolescent and adult care within clinical networks.

281

282 **Key messages**

- 283 1. Length of time to achieve a diagnosis of JSLE varies widely.
- 284 2. These data suggest that JSLE patients experience multiple referrals
285 before accessing paediatric rheumatology care.

286

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