Short running head: Ethnicity and NLE risk

Title: “Ethnicity and Neonatal Lupus Erythematosus Manifestations Risk in a Large Multi-Ethnic Cohort”

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Abstract:

Objective: To evaluate the association between ethnicity and neonatal lupus erythematosus (NLE), as well as specific NLE manifestations in a large multi-ethnic population.

Methods: We conducted a cohort study of the children (≤1 year of age) seen in the NLE clinic at SickKids, between January 2011 and April 2019. The cohort was divided into European, non-European and Mixed European–Non-European groups according to parent reported child’s ethnicity (Canada census categories). Outcomes were NLE and specific NLE manifestations (cardiac, cutaneous, cytopenias, transaminitis and macrocephaly). The frequency of NLE and specific manifestations were compared between ethnic groups (Fisher’s exact test). We tested the association between ethnicity and 1) NLE risk and 2) specific NLE manifestations with logistic regression models, including covariates for child’s sex, maternal rheumatic disease status during pregnancy, and maternal use of antimalarials during pregnancy (multiple comparisons threshold p-value<0.008).

Results: We included 324 children born to 270 anti-Ro antibody positive mothers. Median age at first visit: 1.8 months (IQR: 1.4, 2.3 months). Median follow-up time: 12 months (IQR: 2.24 months). The majority were non-European (48%), with 34% European, and 18% Mixed European–Non-European. There was no significant association between non-European ethnicity (OR 1.14, 95% CI:0.69-1.89, p=0.59), Mixed European-Non-European ethnicity (OR 1.06, 95% CI:0.55-2.06, p=0.84) and NLE risk compared with European ethnicity. We also
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did not find an association between ethnicity and specific NLE manifestations, in univariate or multivariable adjusted models.

Conclusion: In a large multiethnic cohort, there was no association between child’s ethnicity and NLE risk, nor specific NLE manifestations.
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Introduction:

Neonatal lupus erythematosus (NLE) is a passively acquired autoimmune disorder secondary to the transplacental passage of maternal anti-Ro. These antibodies are present in 90% of women with Sjögren’s syndrome (SS) and in 20-30% of women with systemic lupus erythematosus (SLE).

Despite the high prevalence of anti-Ro antibodies in women with rheumatic diseases, 50% of children with NLE are born to asymptomatic women (25%) or women with an undifferentiated autoimmune syndrome (25%).

NLE is characterized by cardiac and non-cardiac manifestations. Cardiac NLE may manifest as conduction tissue disease (congenital heart block, sinus bradycardia), endo-myocardial disease (myocarditis, dilated cardiomyopathy, valvular abnormalities, and endocardial fibroelastosis) or both. The non-cardiac NLE manifestations are cutaneous rash, elevated liver enzymes, cytopenias and benign macrocephaly. The non-cardiac manifestations, except benign macrocephaly, are usually transient and spontaneously resolve with clearance of maternal anti-Ro antibodies.

The most severe NLE manifestation is congenital complete heart block (CHB), which is irreversible. NLE is the most common cause of CHB, accounting for >90% of perinatal cases. CHB is present in 1-5% of children born to women with high-titer anti-Ro antibodies. The risk of CHB increases to up to 18% for children born to women with a previous child with
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Although the presence of maternal anti-Ro antibodies are necessary for NLE, (6) it is not the sole risk factor causing NLE, since the majority of children born to anti-Ro antibody positive mothers are unaffected. The risk of NLE is likely influenced by other factors such as anti-Ro antibody titers,(6) and maternal rheumatic disease status during pregnancy.(7) It has also been demonstrated that maternal antimalarial use during pregnancy reduces the risk of cardiac NLE as well as cutaneous NLE.(8-11)

Previous studies have suggested that ethnicity may also influence NLE outcomes with more frequent adverse cardiac NLE outcomes reported among children of Non-European ethnicity compared to children of European ethnicity. (7),(12) No study to date has examined the association between ethnicity and non-cardiac NLE manifestations. The aim of this study was to examine the association between ethnicity and NLE, as well as specific NLE manifestations, within a large, multi-ethnic, single-centre cohort.

Patients and Methods

Study population

We conducted a cohort study of all patients followed in our NLE clinic at The Hospital for Sick Children, born to women with positive anti-Ro antibodies and seen at ≤1 year of age, between January 2011 and April 2019. The clinic serves a multi-ethnic, greater Toronto area population. Mothers found to be anti-Ro antibody positive as part of a rheumatic disease diagnosis, maternal history of symptoms prompting auto-antibody testing and/or delivery of a
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prior child with NLE were eligible for the study. The anti-Ro antibody status of all mothers was confirmed in the first trimester of pregnancy. Serial fetal echocardiograms were performed beginning at 16-18 weeks gestational age and throughout the pregnancy at intervals determined by antibody titer and echocardiogram findings. Postnatally, children born to these mothers were seen in the NLE clinic at 2, 4 and if necessary at 12 months of age, irrespective of the presence or absence of NLE manifestations. At the first NLE clinic visit we complete EKGs on all infants, along with complete blood counts, liver function tests and auto-antibody tests. If abnormal, these studies are repeated until normalized. At each visit, weight, length and head circumference are measured. A head circumference increasing disproportionately faster than weight and length prompts further investigations such as a head ultrasound. Clinical and laboratory manifestations of NLE were prospectively collected and stored in a dedicated NLE database. Beginning in 2011, families were routinely asked to report mother’s and child’s ethnicity.

Study participants were excluded if missing any of the following: (1) documentation of positive anti-Ro antibodies during pregnancy; (2) self-reported ethnicity for mother and child, or (3) documentation of maternal medication use during pregnancy.

We extracted demographic data on mothers and children from the NLE database and medical charts. Self-reported ethnicity was collected by questionnaire, using Canada Census categories. Participants were grouped based on child’s ethnicity into categories: European, East Asian, South Asian, African, Latin American and Mixed (two or more different
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ethnicities). Subsequently, we stratified the cohort into 3 groups: European, Non-European, and Mixed European – Non-European.

Our outcome, NLE diagnosis, was defined as the presence of one or more of the following manifestations: (1) Cardiac: conduction (congenital heart block, sinus bradycardia) and/or myocardial disease (myocarditis, dilated cardiomyopathy, valvular abnormalities, and endocardial fibroelastosis) (2) Cutaneous: rash of NLE; (3) Hepatic: elevated liver enzymes (level above the age appropriate parameter), (4) Hematologic: hemolytic anemia, neutropenia and/or thrombocytopenia (level below the age appropriate parameter), (5) Neurologic: benign macrocephaly confirmed by head ultrasound with findings consistent with NLE (extra-axial fluid and normal ventricular sizes). We also studied each of the NLE manifestations individually. In order to ensure complete capture of transient NLE manifestations, we defined requirements for the age at first visit for NLE rash at 2-4 months of age, cytopenias and transaminitis at ≤ 2 months of age, benign macrocephaly at 4-12 months of age, and CHB at any time prenatally or ≤1 year of age.

We reviewed self-reported maternal rheumatic disease status and antimalarials use during pregnancy. Antimalarials (hydroxychloroquine or chloroquine) use during pregnancy was defined as medication use before pregnancy or started during the first 2 weeks of pregnancy, and continued throughout. We also reviewed the prevalence of anti-La antibodies in our study cohort.
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Demographic, clinical and laboratory data were analyzed using t-tests and Fisher’s exact tests where appropriate. We tested the association between ethnicity and NLE, as well as specific NLE manifestations in logistic models. Multivariable models included covariates for child’s sex, maternal rheumatic disease status during pregnancy (present/absent), and maternal use of antimalarials during pregnancy (taken/not taken).

Sensitivity analyses restricted to the first born child. We also tested the association between maternal ethnicity and NLE risk and NLE manifestations, including history of a prior child with NLE as covariate, and added anti-La antibody status in multivariable models. A Bonferroni corrected p-value <0.008 (adjust for six independent tests) was used for significance. Data analysis was performed using R Version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the Research Ethics Board at SickKids Hospital (REB no. 1000034004).

Results

A total of 339 children were screened for our study. Of those, 15 were excluded due to negative maternal anti-Ro antibodies during the pregnancy, a first NLE clinic visit older than 1 year of age, unavailable ethnicity data or unconfirmed status of antimalarial use during pregnancy. The study cohort included n= 324 children with 51% female (n=165) (Table 1). Of the 324 children, 14% (n=46) were second or third born children, and of those, n=21 had an older sibling with NLE (6.5% of total cohort). Median age at first visit was 1.8 months (IQR: 1.4, 2.3 months) and the majority of children had their first visit at ≤ 6 months of age (98%, n=318). Children were followed for a median duration of 12 months (IQR: 2,24 months).
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Thirty-six percent (n=117) of the children were not seen at 1 year of age. Participants had their first visit within the relevant time window for each NLE manifestation.

The ethnic distribution was 34% European (n=110), 48% Non-European (n=156) and 18% Mixed European-Non-European (n=58). The largest non-European ethnicities were East Asian (31%) and South Asian (27%), followed by African (21%), Latin American (5%) and Mixed non-European ancestry (16%). There were no differences in the age at first visit between ethnic groups (European 2.2, [SD 1.4 months]; Non-European 2.3 [1.8 months]; Mixed European–Non-European 2.3 [SD 1.4 months], P=0.44), or age at last follow-up visit (European 16.9, [SD 16.3 months]; Non-European 17.1 [16.1 months]; Mixed European–Non-European 17.2 [SD 15.3 months], P=0.91).

Over half of the children in our cohort had NLE (54%, n=175), 13% (n=23) with cardiac involvement: 61% of whom had CHB (n=14). The most common NLE manifestation was hepatitis (53%, n=92) (Table 1).

Our study included 270 mothers, with 196 mothers (73%) having a rheumatic disease diagnosis during pregnancy. The most frequent diagnoses were SLE in 66% (n=129/196) and Sjögren’s syndrome in 18% (n=36/196). Of the mothers with rheumatic disease, 52% (n=101/196) reported taking antimalarials during pregnancy compared to 1% (n=1/74) of women without rheumatic disease diagnoses. As expected a higher proportion of mothers with SLE were on antimalarials during pregnancy compared to mothers with other rheumatic diseases (66% vs. 26%, p-value <0.0001).
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during pregnancy was 26% (n=84), anti-La antibody negativity was 41% (n=132) and 33%
(n=108) were missing Anti-La antibody status.

We found no significant difference in NLE risk between non-European (OR 1.18 95% CI 0.71
-1.94, p=0.51), Mixed European-Non-European children (OR 1.13, 95% CI 0.59-2.16,
p=0.70), compared with European children (Table 2). We also did not find an association
between ethnic group and cardiac NLE (Non-European OR 0.53, 95% CI 0.19-1.43, p=0.21;
and Mixed European-Non-European OR 0.91, 95% CI 0.28-2.89, p=0.88), nor cutaneous
NLE (Non-European OR 1.48 95% CI 0.67-3.25, p=0.32; and Mixed European-Non-
European (OR 0.87, 95% CI 0.28-2.67, p=0.81) (Table 2). This held true in univariate and
multivariable adjusted analyses.

Analyses restricted to the first born child resulted in a samples size of n=260 children, with no
significant change in effect of non-European ethnicity on the odds of NLE (OR 1.20, 95% CI
0.69-2.10, p=0.51), or Mixed European-non-European (OR 0.89, 95% CI 0.42-1.86, p=0.76)
compared with European children. Adding anti-La antibody status to multivariable models did
not significantly change the association between ethnicity and NLE or NLE manifestations
(Supplemental Table 1).

Sensitivity analyses testing the association of maternal ethnicity, instead of child’s ethnicity,
also did not demonstrate a statistically significant association with NLE risk nor specific NLE
manifestations. Also, a sensitivity analyses testing the association between children’s
ethnicity and NLE risk and specific NLE manifestations including history of a prior child with
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NLE as covariate, did not demonstrate a statistically significant association (results not shown).

Discussion

In our multiethnic population of children born to anti-Ro antibody positive mothers, we did not observe a statistically significant association between child’s ethnicity and NLE. There was no difference in the odds of NLE, nor specific NLE manifestations between children of non-European, and Mixed European–Non-European ancestry, compared with European ancestry, with and without accounting for child’s sex, maternal rheumatic disease status, and antimalarials use during pregnancy.

The prevalence of NLE manifestations in our population was similar to that reported in the literature, with the exception of hepatic involvement. A total of 53% of the babies we assessed had evidence of NLE transaminitis. The prevalence of NLE transaminitis reported in the literature is approximately 9-25%. Our higher prevalence is likely due to our clinical practice of routine screening of all infants born to anti-Ro positive mothers for hepatic involvement. The prevalence of NLE transaminitis we observed in our population is similar to other prospective studies that routinely monitored liver function in children born to anti-Ro antibody positive mothers close to 3 months of age. In our population, other NLE manifestations such as rash and cytopenias were found with the same frequency as that reported in prior studies. Although neutropenia was the most common hematologic manifestation of NLE (78%), we did not observe any cases of neonatal sepsis in these infants. Thrombocytopenia usually develops within the first week of life, since the first NLE
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Clinic visit is between 4-8 weeks of age, our data may underestimate the prevalence of thrombocytopenia, since 60% of our population had their first visit after 2 months of age. We found that 7% of infants had benign macrocephaly associated with NLE, which is consistent with the frequency reported in the literature of 8-11%.(4)

Previous studies report CHB affecting 2% of first born children to women with positive anti-Ro antibodies, with this percentage increasing to 15-18% in children born to women with a previous affected child with cardiac NLE.(1, 3) The overall prevalence of CHB in our cohort was 4%. This prevalence is consistent with prior prevalence reports since our cohort included not only first born children but also subsequent children born to women with positive anti-Ro antibodies. In our cohort, 21 children (6%) had an older sibling with NLE, and of those, 13 (62%) children had NLE.

Our study findings of no association between ethnicity and NLE, are consistent with a multinational study of hydroxychloroquine effect on cardiac NLE risk in 257 pregnancies of Anti-Ro antibody positive mothers.(8) Pregnancies were identified from US, UK or French registries of mothers with a previous child with cardiac NLE. In this selected population, there was no association between race/ethnicity and cardiac NLE, after accounting for factors including hydroxychloroquine exposure throughout pregnancy (non-white vs. white OR 0.55 [0.21, 1.45] P = 0.22). Our study findings are contrary to one prior study of ethnicity and cardiac NLE, also from our institution. This study of 189 anti-Ro positive mothers referred for prenatal echos in 195 pregnancies, identified 9 cases of cardiac NLE. The study found that
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maternal Asian ethnicity was associated with cardiac NLE (OR: 11.5, CI 1.4, 95.1, p=0.01).(14) Our differing findings may be due to sampling variation.

Ethnicity represents both genetic and environmental factors potentially influencing NLE risk. Prior genetic studies restricted to single ancestral European and Japanese populations identified human leukocyte antigen (HLA) alleles for CHB risk, specifically HLA-DRB1 alleles and DQA1, both of which have been previously associated with SLE susceptibility.(17-19) To date, there are no large, multiethnic studies of NLE in children born to Anti-Ro positive mothers thus no genetic, ancestral specific factors have been identified.

The study findings should be considered in light of some limitations. The modest number of patients with cardiac NLE manifestations (13%) precludes comparisons between Non-European ancestral subgroups (ie: East Asian, South Asian, African ancestries). However modest, our study’s non-European sample size is the largest reported to date for studies of NLE. Since our study cohort was drawn from the NLE clinic attended by infants after delivery, we could not examine the association between ethnicity and intrauterine deaths.

Our study had a number of strengths. This is the first study focused on the association between ethnicity and NLE risk and specific NLE manifestations. The study population was the largest prospective, single-centre study of children born to positive anti-Ro mothers with and without rheumatic disease diagnoses. With the large proportion of anti-Ro positive mothers without a rheumatic disease, we were able to examine the attributable risk of maternal disease status and medication exposure with NLE. Since our data was
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prospectively collected from infants undergoing routine screening for NLE manifestations, our reported prevalence of NLE and specific manifestations likely reflects the true prevalence of NLE in children born to mothers positive for anti-Ro antibodies.

In conclusion, in this large multiethnic single-centre cohort study of children born to anti-Ro antibody positive mothers, the child’s ethnicity was not associated with NLE risk, nor specific NLE manifestations. Further studies in multiethnic cohorts are needed to validate our findings. Future genetic studies will enable identification of more precise mechanisms influencing NLE risk and manifestations.
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References

Table 1: Child demographic and neonatal lupus erythematosus manifestations (n=324)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n= 324 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female sex</strong></td>
<td>165 (51)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>110 (34)</td>
</tr>
<tr>
<td>Non-European(^a)</td>
<td>156 (48)</td>
</tr>
<tr>
<td>Mixed European-Non-European</td>
<td>58 (18)</td>
</tr>
<tr>
<td><strong>NLE</strong></td>
<td>175 (54)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>23 (13)</td>
</tr>
<tr>
<td>1(^{st}) degree CHB</td>
<td>2 (9)</td>
</tr>
<tr>
<td>2(^{nd}) degree CHB</td>
<td>2 (9)</td>
</tr>
<tr>
<td>3(^{rd}) degree CHB</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Endocardial fibroelastosis</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>5 (22)</td>
</tr>
<tr>
<td><strong>Hepatic(^b)</strong></td>
<td>92 (53)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>69 (39)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54 (78)(^c)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (16)(^c)</td>
</tr>
<tr>
<td>Neutropenia and thrombocytopenia</td>
<td>4 (6)(^c)</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>37 (21)</td>
</tr>
<tr>
<td>Neurologic (benign macrocephaly)</td>
<td>13 (7)</td>
</tr>
</tbody>
</table>
Data presented as n (%). ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

Median values for neutropenia 0.78 x10^9/L (range 0.26-0.99), thrombocytopenia 98 x10^9/L (63-186), ALT 71 U/L (52-314), AST 97 U/L (77-280).

a Non-European group comprised of patients of East Asian (n=49, 31%), South Asian (n=42, 27%), African (n=32, 21%), Latin American (n=8, 5%) and Mixed Non-European (n=25, 16%).

b Age-adjusted normal values were used

c Shown as percentage of patients with hematologic involvement and not of total cohort
Table 2: Predictors of NLE Risk and Specific Manifestations (n=324)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>NLE OR (95%CI) p-value</th>
<th>Cardiac OR (95%CI) p-value</th>
<th>Cutaneous OR (95%CI) p-value</th>
<th>Hematologic OR (95%CI) p-value</th>
<th>Hepatic OR (95%CI) p-value</th>
<th>Neurologic OR (95%CI) p-value</th>
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<tr>
<td>Child Ethnicity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(European referent):</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non-European</td>
<td>1.18 (0.71-1.94)</td>
<td>0.53 (0.19-1.43)</td>
<td>1.48 (0.67-3.25)</td>
<td>1.40 (0.76-2.60)</td>
<td>1.04 (0.59-1.84)</td>
<td>0.36 (0.10-1.31)</td>
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<td>Mixed European</td>
<td>1.13 (0.59-2.16)</td>
<td>0.91 (0.28-2.89)</td>
<td>0.87 (0.28-2.67)</td>
<td>0.85 (0.36-1.98)</td>
<td>1.39 (0.69-2.81)</td>
<td>0.54 (0.10-2.79)</td>
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<tr>
<td>– Non-European</td>
<td>0.70</td>
<td>0.88</td>
<td>0.81</td>
<td>0.70</td>
<td>0.34</td>
<td>0.47</td>
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<td>Male Sex (Female referent)</td>
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<tr>
<td></td>
<td>0.71 (0.46-1.11)</td>
<td>0.52 (0.21-1.29)</td>
<td>0.98 (0.49-1.95)</td>
<td>0.63 (0.36-1.09)</td>
<td>0.54 (0.33-0.90)</td>
<td>2.35 (0.70-7.88)</td>
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<tr>
<td></td>
<td>P=0.14</td>
<td>P=0.16</td>
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<td>P=0.10</td>
<td>P=0.01</td>
<td>P=0.16</td>
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<tr>
<td>Antimalarials in pregnancy</td>
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<td></td>
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<tr>
<td></td>
<td>0.78 (0.46-1.30)</td>
<td>0.80 (0.24-2.67)</td>
<td>0.68 (0.29-1.55)</td>
<td>0.84 (0.46-1.54)</td>
<td>0.58 (0.32-1.05)</td>
<td>1.46 (0.40-5.38)</td>
</tr>
<tr>
<td></td>
<td>P=0.34</td>
<td>P=0.72</td>
<td>P=0.36</td>
<td>P=0.57</td>
<td>P=0.07</td>
<td>P=0.56</td>
</tr>
<tr>
<td>Maternal rheumatic disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.87 (0.50-1.51)</td>
<td>0.30 (0.11-0.83)</td>
<td>1.00 (0.44-2.27)</td>
<td>2.21 (1.07-4.55)</td>
<td>0.99 (0.55-1.80)</td>
<td>1.10 (0.24-4.96)</td>
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<tr>
<td></td>
<td>P=0.63</td>
<td>P=0.02</td>
<td>P=0.99</td>
<td>P=0.03</td>
<td>P=0.99</td>
<td>P=0.90</td>
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</table>

Multivariable models adjusted for child’s ethnicity, sex, antimalarial use during pregnancy, and maternal rheumatic disease status. NLE: neonatal lupus erythematosus, OR: odds ratio, 95%CI: 95% confidence interval
Figure 1. Prevalence of NLE and NLE manifestations stratified by ethnicity

Figure 1 demonstrates the proportions (%) of NLE manifestations in each ethnic group (European, Non-European and Mixed European-Non-European) according to child ethnicity. In the total cohort, the NLE manifestations were hepatitis (53%), hematologic (39%), cutaneous (21%), cardiac (13%), neurologic (7%). NLE: neonatal lupus erythematosus.