**3,800 characters (without spaces), tables uploaded as figures of 300 dpi**

**Title:** Estimated late health outcomes in children diagnosed with mature B-cell non-Hodgkin lymphoma treated with contemporary LMB chemotherapy: A report from the Childhood Cancer Survivor Study (CCSS)

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**Introduction:** Since the mid-1990's, overall survival rates for children diagnosed with mature B-cell non-Hodgkin lymphoma (B-NHL) have exceeded 90%, due in large part due to the widespread utilization of standard LMB chemotherapy. As a result, a population of survivors living beyond 5 years from diagnosis and treatment with LMB is emerging, providing the first opportunity to study late-occurring and chronic health outcomes following contemporary treatment.

**Methods:** Late health outcomes and health status were self-reported among CCSS participants who were 5-year survivors of childhood B-NHL and whose treatment exposures were consistent with LMB-defined risk-groups (A - low; B - intermediate; and C - high risk). Combinations of individual chemotherapy agents (cyclophosphamide [CPM], vincristine, prednisone, doxorubicin [doxo], high-dose methotrexate [HD-MTX], cytarabine, and etoposide) and respective cumulative doses (for CPM, doxo, HD-MTX, and etoposide) were identified from medical record abstraction. Chronic health conditions occurring ≥5 years from cancer diagnosis were graded per the Common Terminology Criteria for Adverse Events (version 4.03). Decreased fertility was defined as failure to achieve or sire a pregnancy after ≥1 year of trying among survivors of childbearing age (15-44 years). Standardized mortality ratios (SMRs) were estimated and Cox regression models (adjusted for sex and race) provided hazard ratios (HR) and 95% confidence intervals (CI) of health conditions compared to a sibling comparison group (n=4,023).

**Results:** Among 94 B-NHL survivors (median age 10 [range 2-20] at diagnosis, 24 years of age [10-39] at evaluation, median follow-up of 14 [7-26] years), pertinent exposures (mean ± standard deviation) included: Group A (n=19) CPM=2,111 +/- 497 mg/m$^2$and doxo=105 +/- 23 mg/m$^2$; Group B (n=46) CPM=4,528 +/- 1,075 mg/m$^2$, doxo=165 +/- 23 mg/m$^2$, and HD-MTX=14,309 +/- 1,413 mg/m$^2$; and Group C (n=29) CPM=5,514 +/- 1,082 mg/m$^2$, doxo=237 +/- 42 mg/m$^2$, HD-MTX=23,301 +/- 5,152 mg/m$^2$, and etoposide=2,146 +/- 1,043 mg/m$^2$. Compared to siblings, survivors were more likely to be male (79% vs. 48%, p<0.001), younger at evaluation (24.3 +/- 6.1 vs. 26.7 +/- 9.2 years, p<0.001), and non-white race (22% vs 13%, p=0.006).

Thirty-five (37%) survivors had ≥1 chronic health condition (grades 1-5); a 4-fold increased risk (HR 4.1, 95% CI: 2.9-5.8) compared to siblings (Group A HR 2.6, 95% CI 1.2-5.6, Group B HR 5.2, 95% CI 3.1-8.6, and Group C HR 4.2, 95% CI 2.4-7.6). The most frequently occurring conditions were obesity (24%) and decreased fertility (10%). Excluding these, Group B (HR 5.3, 95% CI 1.6-17.3), and Group C (HR 5.7, 95% CI 1.7-19.0) survivors remained at increased risk of having ≥1 chronic condition: Group A survivors showed a similar HR without statistical significance (HR 4.0, 95% CI 0.5-31.3). Three survivors died during study follow-up (SMR 6.5, 95% CI 1.3-19.0), only one died due to a non-cancer related cause of death.

Group B survivors were more likely than siblings to report poor general (OR 5.1, 95% CI 2.2-11.9) and Groups B and C were more likely to report poor mental health (OR 2.9, 95% CI 1.0-8.6 and 3.7 95% CI 1.0-12.9, respectively) and impaired functional status (OR 4.5, 95% CI 1.5-13.1, 15.1 95% CI 6.0-37.8). Group A survivors were only more likely to report impaired functional status (OR 11.2, 95% CI 3.5-35.6). No associations with activity limitations (p's>0.1) or sociodemographic differences (educational level < college degree, p's>0.1; household income < $60,000/year, p's>0.1) were identified. Cancer-related pain and anxiety did not differ in Groups B or C compared to survivors in Group A (p=0.9 and 0.2, respectively).

**Conclusions:**
Despite excellent survival rates, children diagnosed with B-NHL and treated with contemporary LMB chemotherapy are at risk for chronic health conditions and health status limitations by 14 years from diagnosis. Studies exploring the trajectory of these findings and the impact of early interventions are needed to inform future frontline treatment protocols.

**Table 1.** Prevalence and hazard ratios for chronic health conditions in survivors and siblings

| | Survivors | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Group A (n=19)** | | **Group B (n=46)** | | **Group C (n=29)** | | **All (n=94)** | | **Siblings (n=4,023)** | | **HR (95% CI) (All survivors vs. siblings)** | **P value** |
| **Overall chronic health conditions** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | | |
| Any disorder, grade 1-5 | 7 | (37) | 16 | (35) | 12 | (41) | 35 | (37) | 862 | (22) | 4.1 (2.9-5.8) | <0.001 |
| | | | | | | | | | | | | |
| **Specific health disorders** | | | | | | | | | | | | |
| Stroke | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 9 | (<1) | 0 | 0.99 |
| Growth hormone deficiency | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 7 | (<1) | 0 | 0.99 |
| Cataracts | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 14 | (<1) | 0 | 1.00 |
| Decreased fertility | 2 | (11) | 3 | (9) | 3 | (10) | 8 | (10) | 278 | (7) | 3.1 (1.5-6.3) | 0.002 |
| Obesity | 5 | (5) | 10 | (27) | 8 | (28) | 23 | (24) | 569 | (14) | 3.7 (2.4-5.7) | <0.001 |
| Hypothyroidism | 0 | (0) | 1 | (2) | 1 | (3) | 2 | (2) | 75 | (2) | 4.3 (1.0-18.2) | 0.05 |
| Cardiomyopathy | 0 | (0) | 0 | (0) | 1 | (3) | 1 | (1) | 9 | (<1) | 13.8 (1.5-123.9) | 0.02 |
| Osteoporosis or osteopenia | 1 | (<1) | 2 | (4) | 1 | (3) | 4 | (4) | 10 | (<1) | 59.3 (15.4-228.6) | <0.001 |