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**Actual prognosis during follow-up of survivors of B-cell non-Hodgkin lymphoma in the Netherlands**

Saskia A.M. van de Schans,¹ Liza N. van Steenbergen,² Jan Willem W. Coebergh,²,³ Maryska L.G. Janssen-Heijnen,²,⁴ and Dick Johan van Spronsen⁵,⁶

¹Dept. of Registry and Research, Comprehensive Cancer Center the Netherlands, Utrecht, the Netherlands; ²Eindhoven Cancer Registry, Comprehensive Cancer Center South, Eindhoven, the Netherlands; ³Dept. of Public Health, Erasmus University Medical Center Rotterdam, the Netherlands; ⁴Dept. of Clinical Epidemiology, Viecuwi Medical Center, Venlo, the Netherlands; ⁵Dept. of Oncology, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands; and ⁶Dept. of Oncology, Radboud University Medical Center, Nijmegen, the Netherlands

**ABSTRACT**

Survival rates determined at diagnosis are often too negative for cancer survivors. Conditional relative survival reflects actual prognosis during follow-up better. Data from all 54,015 patients newly diagnosed in the Netherlands with B-cell non-Hodgkin lymphoma during 1989-2008, aged 15-89 years (Netherlands Cancer Registry), were used. Five-year conditional relative survival was computed for every additional year of survival up to 16 years after diagnosis, according to entity, grade, gender, age, and Ann Arbor stage. The prognosis for survivors of indolent B-cell non-Hodgkin lymphoma improved slightly with each additional year survived up to 91%. For patients with aggressive non-Hodgkin lymphoma conditional relative survival improved strongly during the first year after diagnosis (from 48% to 68%) and gradually thereafter to 93% after 16 years. There were differences between morphological entities. Initial differences in conditional relative survival at diagnosis between groups with different disease stages became smaller with increasing number of years survived. Age remained a prognostic indicator, also after prolonged follow-up. These results help caregivers to plan optimal surveillance and inform patients about their actual prognosis during follow-up. Long-lasting excess mortality among patients with B-cell non-Hodgkin lymphoma indicates the need for additional care long after their diagnosis.

**Introduction**

Mature B-cell non-Hodgkin lymphoma (NHL) is the most common hematologic malignant neoplasm in adults in most populations worldwide.¹ The incidence of indolent NHL has increased since 1989 in the Netherlands, but that of aggressive neoplasms has remained stable.² The incidence of NHL in Europe and the USA has been stable for over 10 years.³,⁴ Survival has increased for patients with mature B-cell neoplasms, resulting in decreasing mortality from these conditions since the beginning of this century. The diverging trends in incidence and mortality have resulted in an increased prevalence of NHL in the Netherlands.²³

There is a clear difference in biological behavior between subtypes of B-cell NHL, which affects survival estimates resulting in an initially better survival for patients with indolent subtypes of B-cell NHL. The ongoing mortality of patients with indolent NHL with prolonged follow-up is most likely caused by further disease progression.⁴⁶

Survival estimates for cancer patients, traditionally reported from the time of cancer diagnosis, are not generally applicable to patients who have already survived for some time after initial diagnosis and treatment. Especially for aggressive NHL these standard survival curves at diagnosis are rather pessimistic since they are based on all patients, including those who died within the first few years.⁷ Conditional relative survival analysis is a method for estimating the survival rate for those who have already survived for a certain period of time.⁷

Such survival estimates seem useful for cancer survivors, yielding more relevant information about their current prognosis, which can be used for personal health-related planning and by treating physicians for planning optimal cancer surveillance.⁸,⁹ Furthermore, they give information about excess mortality which might be caused by either the underlying NHL, late treatment-related toxicity, and/or co-morbidity. Most previous studies on conditional survival for patients with NHL did not subdivide between the distinct entities of NHL,¹⁰-¹² except one study on diffuse large B-cell lymphoma that displayed conditional survival up to 5 years after diagnosis.¹³ It is, however, obvious that better information would be provided by subdividing these entities, each with a different prognosis.

With the marked increase in the number of NHL patients and their improving survival, there is a growing need for a more up-to-date and subgroup-specific analysis of actual survival. In this study we estimated conditional 5-year relative survival rates for B-cell NHL patients, according to morphological entity, grade, gender, age, and stage at each additional year survived up to 16 years after diagnosis.

**Methods**

**Data collection**

The population-based data used were from the nationwide Netherlands Cancer Registry.¹⁴ Information on patients’ characteristics as well as tumor characteristics such as morphology,¹⁵ and Ann Arbor...
Table 1. Number of patients per entity of B-cell non-Hodgkin lymphoma in the Netherlands 1989-2008

<table>
<thead>
<tr>
<th>Group</th>
<th>WHO classification</th>
<th>Number of patients</th>
<th>Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>13,549</td>
<td>CLL</td>
</tr>
<tr>
<td></td>
<td>B-cell prolymphocytic leukemia</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splenic marginal zone lymphoma</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extranodal marginal zone lymphoma</td>
<td>2,196</td>
<td>MZL</td>
</tr>
<tr>
<td></td>
<td>Nodal marginal zone lymphoma</td>
<td>432</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia</td>
<td>990</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoplasmacytic lymphoma</td>
<td>3,425</td>
<td>LPL</td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma, grade I-II</td>
<td>6,802</td>
<td>FL</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous follicle center lymphoma</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td>Follicular lymphoma, grade III</td>
<td>912</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mantle cell lymphoma</td>
<td>2,440</td>
<td>MCL</td>
</tr>
<tr>
<td></td>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>17,010</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary DLBCL of the central nervous system</td>
<td>1,011</td>
<td>DLBCL</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous DLBCL, leg type</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary mediastinal large B-cell lymphoma</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary effusion lymphoma</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma</td>
<td>616</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other, unclassifiable B-cell neoplasms</td>
<td>3,408</td>
<td></td>
</tr>
</tbody>
</table>

since diagnosis (around 70%). The prognosis of CLL started to improve after 9 years (from 71% to 81% after 14 years). CRS improved greatly for DLBCL survivors during the first year after diagnosis (from 48% at diagnosis to 71% after 1 year). In the additional years after diagnosis the improvement in the prognosis of DLBCL patients leveled off, but became slightly higher (87% after 10 years) than that of patients with the indolent B-cell NHL subtype CLL (74% after 10 years) (Figure 1). MCL survivors had the worst prognosis of patients with all entities, although this prognosis gradually improved with each additional year survived after diagnosis (from 40% at diagnosis to 68% after 6 years). The patterns of CRS for indolent and aggressive B-cell NHL were similar for males and females (data not shown). However, a significantly better CRS was found for female patients with CLL compared to male patients with CLL (Table 2).

Five-year relative survival at diagnosis was better for younger patients than for elderly patients for both indolent and aggressive NHL (at diagnosis: 88% for those 15-
44 years versus 59% for those 75-89 years with indolent NHL (P < 0.05) and 69% for those 15-44 years versus 51% for those 75-89 years with aggressive NHL (P < 0.05). This initial difference in relative survival between patients in different age groups remained among patients with both indolent and aggressive NHL (CRS after 5 years: 90% for those 15-44 years versus 66% for those 75-89 years with indolent NHL (P < 0.05) and 94% for those 15-44 years versus 75% for those 75-89 years with aggressive NHL (P < 0.05)). Similar results were found for all examined entities of NHL (Figure 2A-D). Age does, therefore, remain an important prognostic factor.

As expected, patients with higher stages of FL had a poorer CRS at diagnosis than patients with lower stages of FL (86% (stage I-II) versus 66% (stage III-IV, P < 0.05)). This initial difference in survival at diagnosis between stage groups for patients with FL decreased somewhat with time survived since diagnosis, but remained statistically significant (CRS after 10 years: 92% versus 77%, P < 0.05) (Figure 3A). For patients with DLBCL a similar difference in CRS at diagnosis was found (64% for stage I versus 88% for stage II-IV, P < 0.05), which largely disappeared after patients had survived for 5-10 years (after 10 years: 88% versus 86%) (Figure 3B).

For indolent and aggressive NHL 3-year relative survival at diagnosis was significantly better in 2003-2008 than in 1995-2000 (3-year relative survival at diagnosis was 79% for 15-44 years versus 45-59 years versus 60-74 years versus 75-89 years with indolent NHL (P < 0.05) and 77% for those 15-44 years versus 66% for those 75-89 years with aggressive NHL (P < 0.05) versus 65% for those 75-89 years with aggressive NHL (P < 0.05)). Similar results were found for all examined entities of NHL (Figure 2A-D). Age does, therefore, remain an important prognostic factor.

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versus 85% for indolent NHL and 49% versus 60% for aggressive NHL; both \( P<0.05 \). This difference in survival decreased with years since diagnosis, especially for aggressive NHL (Figure 4).

Minimal excess mortality (CRS >95%) only occurred in younger patients (15-44 years) with MZL from diagnosis, DLBCL from 6 years after diagnosis and FL for those who had already survived for 15 years after diagnosis. For all other groups of NHL patients survival remained lower compared to that in the general population.

**Discussion**

The prognosis for survivors with any subtype of indolent B-cell NHL improved slightly, up to 80-90%, with each additional year of survival after diagnosis. For patients with DLBCL CRS improved markedly during the first year after diagnosis (from 48% at diagnosis to 71%) and thereafter gradually to 95% after 16 years. Differences in survival by gender were small. Age remained a prognostic indicator, also after prolonged follow-up. Initial differences in CRS at diagnosis between groups with different stages of disease became smaller with increasing number of years survived.

To the best of our knowledge, this is the first study reporting separately on conditional 5-year relative survival for several entities of NHL and for the subgroups of patients with indolent or aggressive mature B-cell NHL alive up to 16 years after diagnosis according to age, gender, and Ann Arbor stage. We were able to compute up-to-date and detailed CSR using high-quality data from the long-standing Netherlands Cancer Registry, and by application of period analysis. The results give insight into excess mortality for each additional year after diagnosis a group of NHL patients has survived.

For indolent lymphoma conditional survival rates improved slightly in the years following diagnosis but remained lower than those in the general population. This probably reflects the natural history of this chronic disease. Patients with indolent lymphomas have mostly been managed by a primary wait-and-see strategy without the achievement of a long-lasting complete remission.\(^{24-26}\) This strategy is more common in CLL and LPL patients than in MZL and FL patients. This is reflected by the larger improvement in prognosis in patients with the latter entities. In the younger age group of patients with the indolent B-cell NHL entities FL and MZL minimal excess mortality was observed, suggesting cure of their disease at diagnosis for MZL and 15 years after diagnosis for FL. Unfortunately, we could not pin down any association with treatment, because we could not document the exact therapy or therapies of each patient and subgroups would have become too small for analysis.

For patients with DLBCL survival improved greatly during the first years after diagnosis, resulting in a better prognosis 1-4 years after diagnosis, which is in line with the main treatment goal in this disease: achievement of a sustained complete remission. The long-term prognosis of individuals with DLBCL became similar to that of the general population for younger patients who had survived for 6 years. This suggested that many patients can be considered cured. However, after prolonged follow-up relevant cardiovascular and second tumor effects cannot be excluded. A remaining excess mortality among NHL patients aged 45 years or older also appeared in some studies from Europe, as well as Canada and Australia.\(^{10,12}\) Late recurrences of lymphoma are likely as well as late effects of chemotherapy and radiotherapy (mainly cardiovascular disease and secondary tumors).\(^{25,26}\) Furthermore, a large proportion of NHL patients reported a high level of fatigue up to 10 years after diagnosis.\(^{27,28}\) The gradual improvement in prognosis for patients with MCL could indicate that secondary therapies resulted in cure for some of these individuals.

Survival of patients with B-cell NHL depends on several pretreatment prognostic variables.\(^{5,30-32}\) In this study the prognostic effect of Ann Arbor stage at diagnosis decreased with time since diagnosis. In other words, conditional survival improved more with time since diagnosis in the groups with more advanced stage disease. This decrease in prognostic value of stage (and probably also

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![Figure 3](image-url) **Figure 3.** (A) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with follicular lymphoma, according to Ann Arbor stage. (B) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with diffuse large B-cell lymphoma (including central nervous system, cutaneous, mediastinal), according to Ann Arbor stage.
other disease-related prognostic factors) during follow-up is in line with the known natural behavior of the disease, especially of aggressive NHL. Initially mortality is largely due to disease progression. For those who survive this period the disease is either in complete remission because of successful therapy or the less aggressive clinical behavior results in a decreased impact of disease-related prognostic factors. This decrease of impact of stage on survival during follow-up confirms the earlier published observations of Moller et al. in DLBCL patients.13

In contrast, age at diagnosis remained of prognostic value in our study during prolonged follow-up. The negative effect of older age on long-term survival generally reflects the reduced ability of older patients to tolerate intensive salvage therapy, the age-related propensity for late doxorubicin-induced cardiomyopathy, but also increased mortality from co-morbidity.31,33-37

The prognosis of B-cell NHL patients has improved in recent decades due to the introduction of more effective drugs for newly diagnosed and relapsed patients (e.g. rituximab),38,39 to which the large scale HOVON trials may have contributed in the Netherlands. Furthermore, research towards more accurate diagnostics, better prognostication, and better supportive care could have improved the prognosis of patients diagnosed in more recent years. This appears to be reflected in our data. Understandably, the direct effect of these therapies, diagnostics, and prognostication on conditional survival could not be demonstrated in this population-based study.

Long-term follow-up is required to calculate clinically informative measures of conditional survival. The Netherlands Cancer Registry has collected population-based data since 1989, thus long-term follow-up information is available. However, a changing classification system, improvements in disease detection and evolving cancer registration procedures may have contributed to temporal trends in incidences of lymphoma entities.40 Variation in the incidence of entities of lymphoma over time could have resulted in differences in prognosis per period of diagnosis.

A web-based tool has been constructed to make conditional relative survival estimates available for physicians treating cancer patients. A user-friendly program provides insight into CRS estimates for every additional year after diagnosis survived for several tumor sites, including indolent and aggressive NHL, according to gender and age at diagnosis. This program (www.dutchcancersurvival.com) is available for caregivers, for counseling their patients, e.g. concerning the planning of their remaining life. However, they should of course also consider the actual condition of the patient.

In conclusion, with the marked increase in the number of NHL survivors there is a growing need for information of actual prognosis during follow-up, which is provided by conditional survival figures. These figures can help caregivers to plan optimal cancer surveillance and patients to get on with the planning of their remaining life. Long-lasting excess mortality for B-cell NHL patients indicates the need for prolonged care following diagnosis, with a consequent impact on patients and the healthcare system.

Acknowledgments
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Authorship and Disclosures
Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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