




# Age is the most important predictor of survival in diffuse large B-cell lymphoma patients achieving event-free survival at 24 months: a Swedish population-based study

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## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma in Europe constituting 30–58% of all lymphoma series.<sup>1,2</sup> It is the commonest lymphoma in Sweden with almost 700 cases/year.<sup>3</sup> The standard therapy for DLBCL remains anthracycline-based chemotherapy CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOEP (CHOP plus etoposide) in addition

## Summary

Routine follow-up for diffuse large B-cell lymphoma have been shortened to 2 years when event-free survival at 24 months (EFS24) emerged as a new milestone. In the present study, we aimed to determine whether the achievement of this milestone affected overall survival (OS). We compared OS to that of an age- and sex-matched population, analysed other factors governing OS, and reviewed the causes of death. Data were collected from the Swedish Cancer Registry and from individual patient's records. We included 1169 adult patients from five counties between the years 2001 and 2014. The median (range) age was 64.6 (18–91) years, 56.6% were men and the median follow-up was 82.3 months. For early stages, the achievement of EFS12 did not improve OS. More than two-thirds of the patients (n = 837, 71.6%) achieved EFS24, of which 190 (22.7%) died during follow-up. Lymphoma (20%), cardiovascular disease (22.4%) and malignancies (16%) contributed to causes of death. Patients aged <60 years had an OS that matched the standard population. In multivariate analysis, only age >60 years significantly affected OS after EFS24 compared with the standard population. We concluded that follow-up beyond EFS24 should be considered for patients aged >60 years.

**Keywords:** DLBCL, EFS24, age, OS.

to the monoclonal antibody rituximab. In elderly patients, the addition of rituximab to chemotherapy improves the 10-year overall progression-free survival (PFS) and overall survival (OS) by >16%.<sup>4</sup> The beneficial effect of rituximab was also confirmed for younger patients with good prognostic factors.<sup>5</sup> However, more than one-third of the patients eventually relapse or progress.<sup>6,7</sup> Well-established risk factor-based group classification, such as the International Prognostic Index (IPI) and Age Adjusted IPI (aaIPI) and Revised IPI

(R-IPI), have been used historically to predict OS or PFS.<sup>8–10</sup> Standard follow-up after completed treatment has routinely been around 5 years. Newer personalised risk prediction models for event-free survival (EFS) at 24 months (EFS24) have emerged<sup>11,12</sup> and there is increasing evidence that 24 months is a sufficient end-point for follow-up.<sup>13,14</sup> Maurer *et al.*<sup>11</sup> reported that patients achieving EFS24 had similar survival as an age- and sex-matched population in the USA and those results were confirmed in a second cohort from France. Interestingly, when looking at the EFS at 12 months (EFS12) milestone poor pretreatment prognostic markers continued to affect survival and prognosis for patients with lymphoma, until they reached EFS24, with the exclusion of Stage I and II. This early stage group had a survival that matched an age- and sex-matched population just after 12 months regardless of pretreatment prognostic factors.<sup>11</sup> In a later study, Maurer *et al.*<sup>15</sup> concluded that the OS of patients achieving EFS24 was marginally lower, but very similar clinically to an age- and sex-matched population in respective countries in a large multicentre international study up to 7 years after achieving that milestone. However, patient inclusion was largely from clinical trial databases and might therefore not reflect real-life DLBCL patient groups as elderly patients and those with comorbidities were excluded. A later Danish population-based study highlighted that only patients aged <50 years achieving EFS24 had similar OS as the age- and sex-matched Danish standard population.<sup>12</sup> Another publication from British Columbia contradicted the aforementioned findings by showing that there was increased risk of death at EFS24 for patients with DLBCL when compared to age- and sex-matched population regardless of age, Stage and IPI risk.<sup>16</sup> Because of the above-mentioned conflicting results, we aimed to confirm whether EFS24 is a robust outcome in an unselected population of patients with DLBCL compared to age- and sex-matched individuals from the Swedish population. Furthermore, we aimed to explore if other clinical variables influenced the achievement of EFS24. We also evaluated EFS12 as a possible outcome predictor for patients with low-stage DLBCL (Stages I and II). We looked at causes of death, mainly if it was lymphoma related or not. Cardiovascular mortality and secondary malignancies were also of special interest, primarily when evaluating the need for follow-up beyond 2 years.

## Patients and methods

### *Study design and setting*

In this retrospective, multi-institutional cohort study patients were included from the Swedish Lymphoma Registry (SLR). Inclusion was from five Swedish counties; Uppsala, West Gotaland, Gavleborg, Sodermanland and Dalarna. Patients from West Gotaland were diagnosed between the years 2004–2012, whereas patients from the other counties were diagnosed between the years 2001–2014. All patients had DLBCL

or high-grade malignant B-cell lymphoma and were treated with rituximab (R)-CHOP or R-CHOP-like regimens with curative intent, i.e. patients treated with less intensive chemotherapy regimens and those who did not receive anthracycline were excluded. Data were collected until November 2018.

### *Patient population*

In total, 1169 adult patients (aged  $\geq 18$  years) were included. Clinical information was both obtained from the SLR and the patients' medical records. Patients with primary central nervous system lymphoma, post-transplant lymphoproliferative disorder and human immunodeficiency virus-positive patients were excluded. However, patients with Burkitt-like DLBCL, mediastinal B-cell lymphoma and discordant lymphomas were included, as were transformed indolent lymphomas provided the indolent lymphoma was untreated. The original pathological diagnosis was not re-evaluated. Patients were followed according to the now outdated Swedish Lymphoma Group guidelines with physical examination and laboratory tests every 3–4 months for the first 2 years, at 6 months for year 3 and annually for years 4 and 5.

Recorded baseline data included: age at diagnosis, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS 0–4), Stage at diagnosis (Ann Arbor I–IV), IPI score, lactate dehydrogenase (LDH; above upper limit normal vs. normal), presence of bulky disease, presence of disease in  $\geq 1$  extra-nodal organ, and type of treatment (R-CHOP or R-CHOEP) and treatment outcome at the end of treatment (complete response, partial response, stable disease or progressive disease), defined according to International Response Criteria<sup>17,18</sup>, were also reported. Applicable dates of relapse/death, cause of death (determined by information in medical records or from death certificates) and the date of last follow-up were obtained. Death during treatment or because of relapse was coded as death due to lymphoma. When death was not due to lymphoma, the causes were grouped into cardiovascular disease, cancer, dementia, others and unclear.

Treatment result was evaluated at 6–8 weeks after therapy termination with computed tomography (CT) in all cases and in some of the cases positron-emission tomography (PET). A partial response was considered as unconfirmed complete response in the analysis, provided the patient did not receive additional therapy. The EFS was estimated from the time of diagnosis to the time of relapse or death. Patients in complete remission (CR) and unconfirmed complete remission (CRu) at end of treatment were included in the EFS group. Patients who died before reaching the aforementioned milestones (EFS24, EFS12 for early stage lymphoma) were excluded from the analysis. The OS was defined as time from date of diagnosis until date of death or last follow-up.

*Reference age- and sex-matched population.* Swedish life tables from Statistics Sweden ([www.scb.se](http://www.scb.se)) state the historical

individual risk of death depending on sex and age per calendar year. A standard population was generated that matched the study population in terms of age and sex. For each individual, probabilities matched on sex, age and index year for each subsequent year was calculated into a cumulative product of a time-series of likely survival for each individual. Subsequently, the survival of the standard population was compared to the survival of the study population.

### Statistical methods

Categorical variables were expressed as number (%) and continuous variables as median (range).

The chi-square test was used for bivariate comparisons of categorical variables. Survival curves with 95% confidence intervals (CIs) were computed using the Kaplan–Meier method. In accordance to statistical methodology no CI was computed for the standard population, as the standard population was based on actual national historical death rates. Overlapping CI intervals were used to examine survival disparities between different cohorts of the study population and the survival of the derived standard population. Survival at different EFS milestones (12 and 24 months) was calculated (including only patients achieving the specified milestone in the analysis). A standardised mortality ratio (SMR) using observed to expected deaths was calculated for 1 and 5 years after achieving the landmark time-point. Cox proportional hazard was used for multivariate analysis including prognostic parameters based on the IPI score. A two-sided  $P \leq 0.05$  was regarded as the cut-off for statistically significant results in comparisons between groups.

Statistical analyses were performed using the R statistical program version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; [www.r-project.org](http://www.r-project.org)). The study was approved by the local Review Board in Uppsala, Sweden.

### Results

In this study group of 1169 patients, the median (range) follow-up was 82.3 (0.4–213) months. The median (range) age was 64.6 (18–91) years and 56.6% were men. The ECOG PS was 1–2 in 48.5%. The IPI score was 3–5 in 44.2% and 58.2% had Stage III–IV. Bulky disease was detected in 23.9%. LDH was elevated in 61.7%. Extra-nodal disease was found in 46.4%. Most of the patients (88.5%) received R-CHOP (Table I).

More than two-thirds of the patients ( $n = 837$ , 71.6%) achieved EFS24 with better OS compared with those who did not (Fig 1A).

The patients not achieving EFS24 ( $n = 332$ , 28.4%) were older (67.6 vs. 63.4 years,  $P = 0.003$ ), tended to have higher IPI scores (3–5) (62% vs. 34.2%,  $P < 0.001$ ) and were more likely to have B symptoms (56.6% vs. 38.6%,  $P < 0.001$ ), bulky disease (31.9% vs. 20.7%,  $P < 0.001$ ) and extra-nodal involvement (55.7% vs. 42.9%,  $P < 0.001$ ). There were no

Table I. Demographic and clinical characteristics.

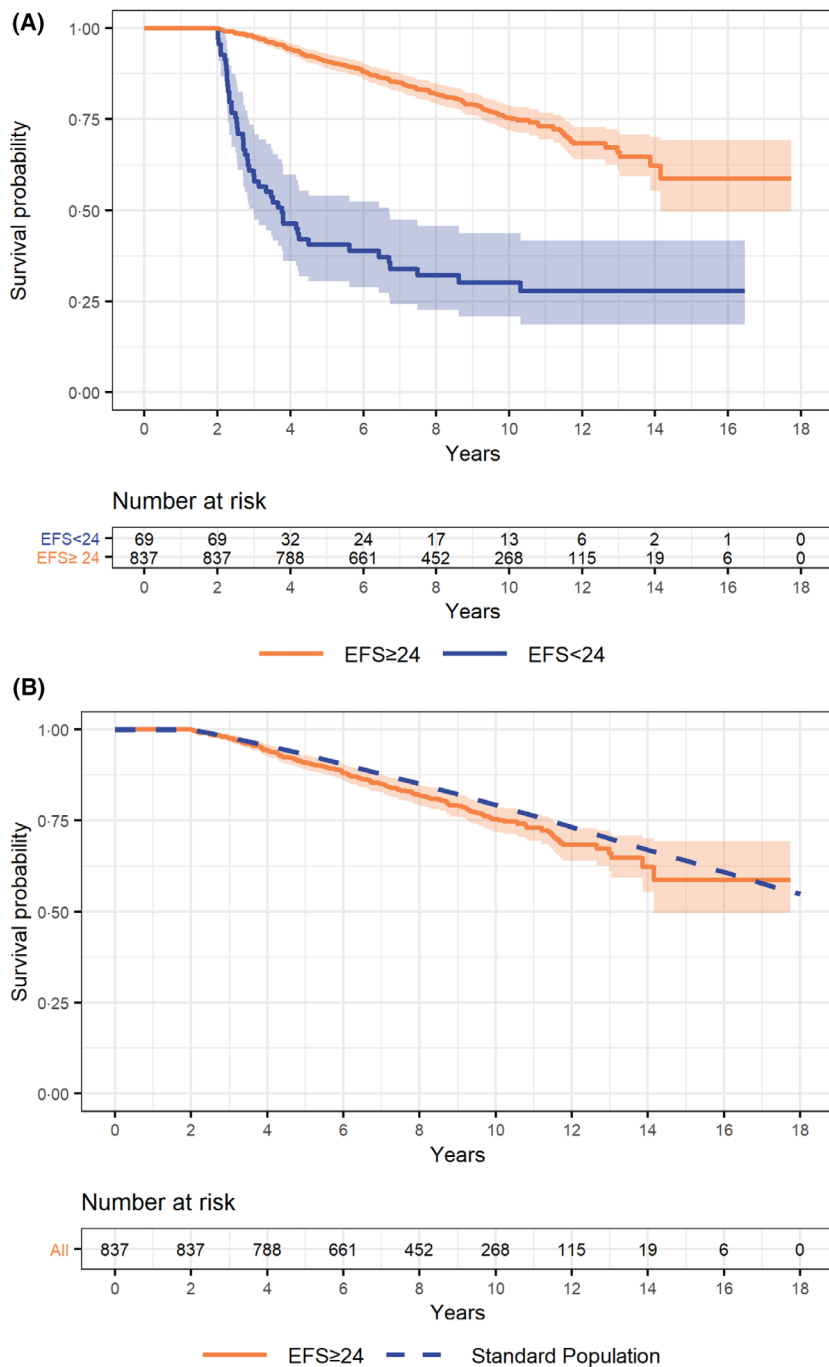
Characteristic ( $N = 1169$ )	Value	Missing data
Age, years, mean (range)	64.6 (18–91)	
Age groups, years, $n$ (%)		
<29	22 (1.9)	
30–39	49 (4.2)	
40–49	89 (7.6)	
50–59	179 (15.3)	
60–69	361 (30.9)	
70–79	333 (28.5)	
>80	136 (11.6)	
Sex, $n$ (%)		
Male	662 (56.6)	
Female	507 (43.4)	
ECOG PS, $n$ (%)		17 (1.5)
0	485 (41.5)	
1–2	572 (48.5)	
3–5	89 (7.6)	
Stage, $n$ (%)		23 (2)
Stage I–II	489 (41.8)	
Stage III–IV	680 (58.2)	
B symptoms, $n$ (%)	511 (43.7)	14 (1.2)
High LDH, $n$ (%)	721 (61.7)	10 (0.9)
Bulky, $n$ (%)	279 (23.9)	2 (0.2)
Extra-nodal disease, $n$ (%)	543 (46.4)	11 (0.9)
IPI score, $n$ (%)		17 (1.5)
0	91 (7.8)	
1–2	544 (46.5)	
3–5	517 (44.2)	
Chemotherapy, $n$ (%)		
CHOP	1034 (88.5)	18 (1.5)
CHOEP	113 (11.2)	
Other	4 (0.3)	
Radiation therapy, $n$ (%)	152 (13)	9 (0.8)

ECOG PS: Eastern Cooperative Oncology Group Performance Status. Extra-nodal disease: involvement of extra-nodal organ. IPI: International Prognostic Index. LDH: lactate dehydrogenase.

significant differences in sex, treatment regimen (R-CHOP vs. R-CHOEP) or the addition of radiotherapy (RT) after R-CHOP treatment between patients achieving EFS24 and those who did not (Table SI).

The OS for all patients with DLBCL was statistically only marginally worse when compared with an age- and sex-matched standard population once EFS24 was reached (Fig 1B): the SMR at 5 years after EFS24 was 1.23 (95% CI 1.02–1.44).

When dividing the study cohort according to age (< or >60 years), we found that patients aged <60 years ( $n = 266$ ) had an OS comparable to the standard population with only nine events occurring up to 5 years after achievement of the EFS24 milestone (Fig 2A, Table SIIIA); the SMR at 5 years was 2.00 (95% CI 0.70–3.27). However, in patients aged >60 years ( $n = 571$ ) there were 110 events at 5 years after EFS24 and OS was worse when compared to the standard population (Fig 2B, Table SIIIB), although statistically not significant: SMR 1.19 (95% CI 0.99–1.39).



**Fig 1.** (A) Overall survival (OS) for patients with diffuse large B-cell lymphoma (DLBCL) who achieved event-free survival at 24 months (EFS24) versus those who did not. Note: Patients with an event prior to 2 years were excluded from the analysis (only applicable for EFS <24 months). (B) OS for patients with DLBCL achieving EFS24 compared with an age- and sex-matched general population. Standardised mortality ratio at 7 years (5 years after relapse-free period) was 1.23 (95% CI 1.02–1.44). [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Age-stratified analysis demonstrated that in the younger patients groups <29, 30–39, 40–49 and 50–59 years, OS matched that of their peers in the standard population (Fig 1A–D). The OS for patients in the age interval 60–69 years was worse compared to the standard population with a SMR of 1.65 (95% CI 1.09–2.18) and even for the older age group

(70–79 years) with a SMR of 1.19 (95% CI 0.88–1.47), although statistically not significant. The OS for patients aged >80 years matched that of their peers without statistical significance, with a SMR of 0.96 (95% CI 0.66–1.21) (Fig S1E–G).

Multivariate Cox regression analyses for patients achieving EFS24 considering risk factors identified by the IPI score,

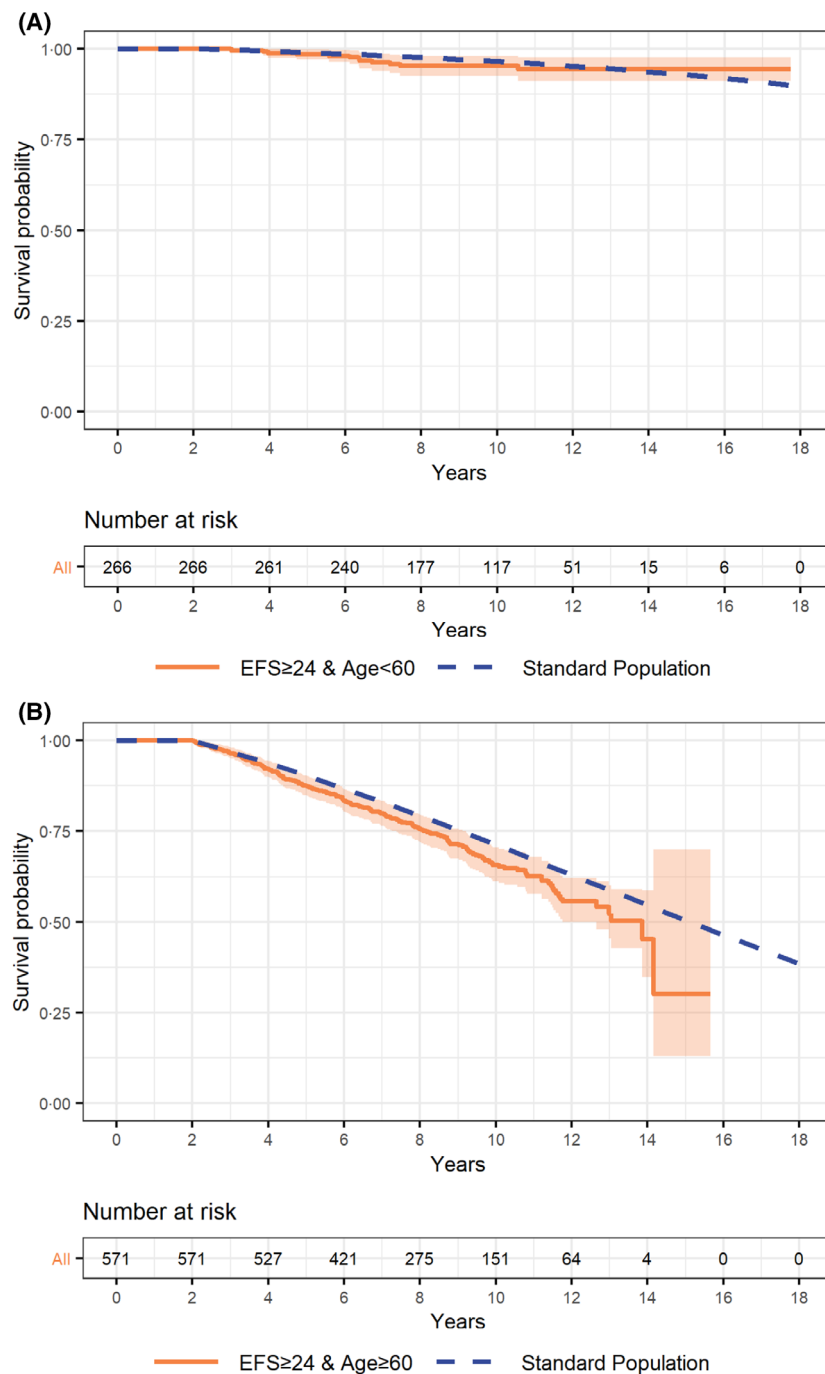


Fig 2. (A) Overall survival (OS) for patients with diffuse large B-cell lymphoma (DLBCL) aged <60 years who achieved event-free survival at 24 months (EFS24) compared with an age- and sex-matched general population. Standardised mortality ratio at 7 years (5 years after relapse-free period) was 2.00 (95% CI 0.70–3.27). (B) OS for patients with DLBCL aged >60 years who achieved EFS24 compared with an age- and sex-matched general population. Standardised mortality ratio at 7 years (5 years after relapse-free period) was 1.19 (95% CI 0.99–1.39). [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

revealed that an age >60 years and ECOG PS of 4 were the only factors significantly affecting survival when compared to other risk factors after EFS24 (Table SII).

Patients with early stage lymphoma (Stage I–II) achieving EFS12 had a worse OS when compared to the matched standard population (Fig 3B): SMR at 5 years after EFS12 was

1.35 (95% CI 1.07–1.62). However, the OS was better compared with patients not reaching EFS12 (Fig 3A).

Of all 1169 patients, 501 (42.9%) patients died. In the EFS24 group, a total of 190 patients died, with 38 (20%) of the deaths attributed to lymphoma. Causes of death for the remaining 152 patients were as follows: cardiovascular disease

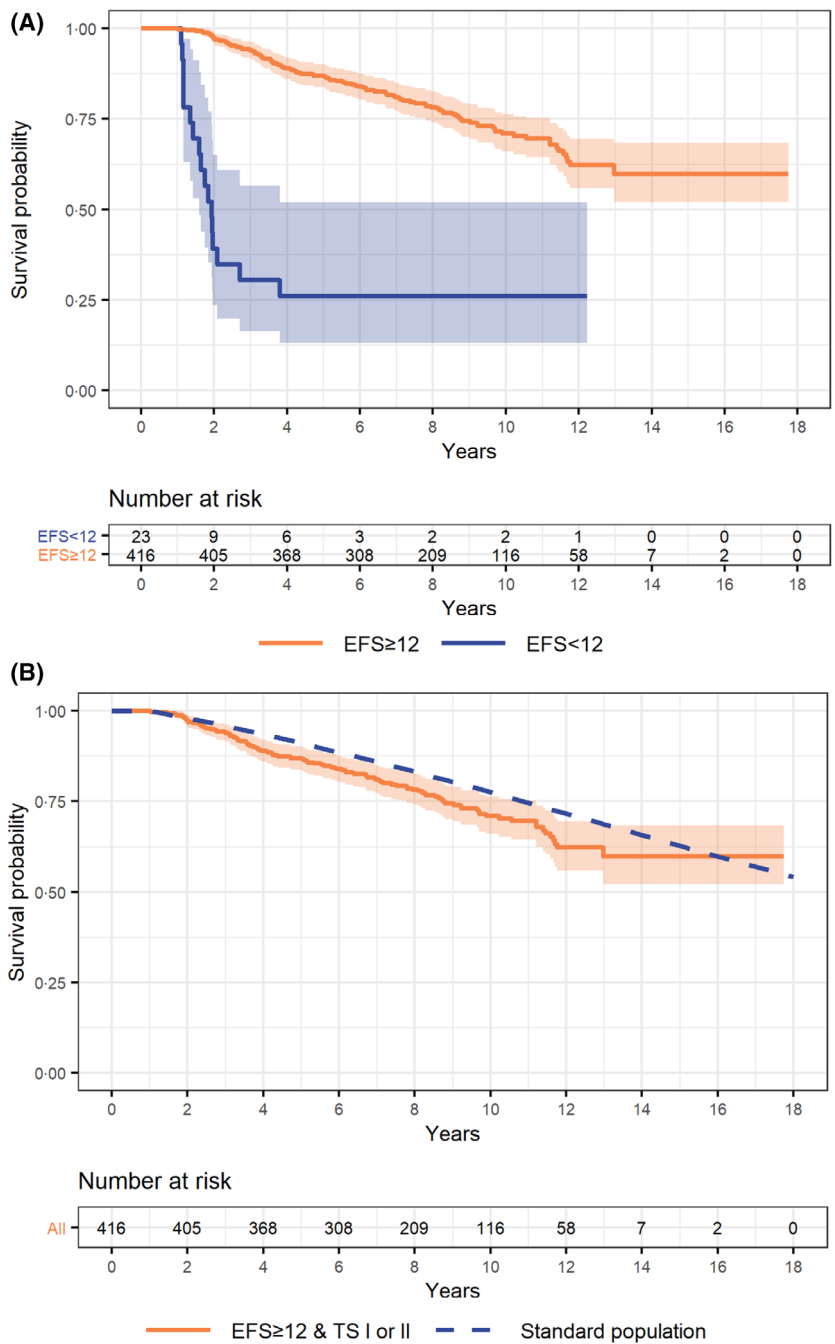


Fig 3. (A) Overall survival (OS) for patients with diffuse large B-cell lymphoma (DLBCL) with Stage (TS) I–II who achieved event-free survival at 12 months (EFS12) versus those who did not. (B) OS for patients with DLBCL with Stage I–II after achieving EFS12 in comparison to an age- and sex-matched general population. Standardised mortality ratio at 7 years (5 years after relapse-free period) was 1.35 (95% CI 1.07–1.62). [Colour figure can be viewed at wileyonlinelibrary.com]

34 (22.4%), cancer 24 (16%), dementia five (3.3%), others six (4%) and unclear 83 (54.6%).

**Discussion**

Maurer *et al.*<sup>11</sup> showed in two study cohorts that newly diagnosed patients with DLBCL treated with standard

immunochemotherapy achieving EFS24 and patients with Stage I and II disease who achieved EFS12 had similar OS to the age- and sex-matched standard population. We found in our present unselected patient cohort that this could only be confirmed for patients aged <60 years who achieved EFS24. Furthermore, patients with early stages (I and II) who achieved EFS12 still had a worse

prognosis in comparison to a matched healthy population.

Our present findings with regards to EFS24 resembles the findings of a Danish population-based study where, in a total of 1621 patients, EFS24 was calculated for those with CR or CRu after initial treatment and with a follow-up of ~8 years. They found that only patients aged <50 years had a normalised OS comparable to an age- and sex-matched Danish population, regardless of other risk factors such as IPI score.<sup>12</sup>

Interestingly, in a large population-based study from British Columbia ( $n = 2046$ ) where EFS24 was calculated from diagnosis, the 5-year risk of relapse decreased after achieving EFS24 (33% to 11%), but OS for EFS24 patients remained worse than that of age- and sex-matched local population regardless of age, IPI score and disease stage. However, a pathological subtype analysis showed that patients achieving EFS24 who had either germinal centre B-cell-like or primary mediastinal B-cell lymphoma did have an OS comparable to the standard population.<sup>16</sup> We did not account for histological subtypes in our present analysis.

In 2019, published data from the Netherlands by Van der Galiën *et al.*<sup>19</sup>, supported Maurer's findings, where patients who achieved PFS24 (319 patients from a total of 585) had an OS that was similar to Maurer's cohort. The follow-up time was >10 years and PFS24 was calculated from the end of treatment. Of the patients achieving PFS24, only 9% relapsed and 18% died. The causes of death were lymphoma relapse in 19%, cardiovascular in 23%, and other malignancies in 25% of the patients.

The difference in OS for patients achieving EFS24 in the aforementioned studies could be due to the different study populations, but might be also partly due to different definitions of EFS (time from diagnosis vs. time from end of treatment) and in inclusion criteria (patient who achieved CR or CRu).

We also found that established risk factors, e.g. older age, poor ECOG PS at diagnosis, presence of bulky disease, extranodal involvement, high LDH and IPI index, all increased the risk of never reaching EFS24. In part, this has previously been reported in a large study with >7000 patients, which determined the loss of life expectancy and found that mainly IPI score >2 significantly had an impact on the outcome.<sup>20</sup>

Despite the missing causes of death, about one-fifth of the patients achieving EFS24 died from cardiovascular disease. Cardiovascular toxicity secondary to treatment with doxorubicin-based chemotherapy is well described, both early after treatment and as a long-term sequel after non-Hodgkin lymphoma (NHL).<sup>21,22</sup> The incidence is largely dependent on the cumulative dose. Factors increasing the risk include age, male sex, previous or concurrent mediastinal RT and presence of other cardiovascular risk factors.<sup>23</sup> The classical clinical presentation is congestive cardiac failure, but subclinical left ventricular dysfunction and cardiomyopathy may well precede the onset of symptoms.<sup>24</sup> The risk of cardiac

dysfunction in patients aged >50 years receiving a cumulative dose of >200 mg/m<sup>2</sup> doxorubicin is estimated to be up to 33% within 1 year of treatment.<sup>25</sup> Long-term risk of congestive heart failure is increased in comparison to the normal population.<sup>22</sup> Long-term follow-up of these patients is thus warranted both for clinical assessment and lifestyle counselling with regards to other risk factors, e.g. smoking, obesity, hypertension and hyperlipidaemia. Early intervention should be considered as it may play an important role in reducing cardiac events.<sup>26</sup>

Patients treated for NHL are known to have an increased risk of secondary malignancies such as leukaemia, lung cancer, renal cancer and bladder cancer.<sup>27</sup> Although some studies have shown no difference in the incidence between patients who received RT and those who did not,<sup>28</sup> RT especially in young females is associated with a higher risk of breast cancer.<sup>29</sup> In our present study, 16% of the patients who died without lymphoma, died due to another cancer.

The strengths of the present study include the population-based design, the long duration of follow-up (17.8 years) and the relatively large number of patients with well-documented data.

In conclusion, EFS24 appears to be an attractive end-point for follow-up, as most lymphoma-related events occur before this milestone. The Swedish Lymphoma Group considers 2 years of follow-up as satisfactory for relapse-free patients with DLBCL. Yet, this may only be valid for patients aged <60 years. More studies are warranted to understand why. In the meantime, we suggest prolonged follow-up for patients aged >60 years, at least at the primary care level, with regards to a possibly increased risk of cardiovascular disease and secondary malignancies.

## Author Contributions

Amal Abu Sabaa: data acquisition, draft of and final approval of manuscript. Charlott Mörth: data acquisition, draft of and final approval of manuscript. Sverker Hasselblom: data acquisition, manuscript review and final approval of manuscript. Gustaf Hedström: statistical analysis, manuscript draft and final approval of manuscript. Max Flogegård: data acquisition and final approval of manuscript. Mimmi Stern: data acquisition. Per-Ola Andersson: data acquisition, manuscript review and final approval of manuscript. Ingrid Glimelius: manuscript review and final approval of manuscript. Gunilla Enblad: data acquisition, manuscript draft and final approval of manuscript.

## Conflict of interest

Amal Abu Sabaa, Charlott Mörth, Sverker Hasselblom, Gustaf Hedström, Max Flogegård and Mimmi Stern: none. Per-Ola Andersson: speaker honoraria from Roche, Gilead and Janssen and has been a consultant for Abbvie, Gilead, Janssen and Roche and received an unrestricted research grant from

Gilead. Ingrid Glimelius: IG honoraria from Janssen and participation in scientific board in a conference organised by Janssen. Gunilla Enblad: speaker honoraria from Roche and Gilead and former member in advisory board for Gilead.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Fig S1.** (A) Overall survival (OS) for patients with diffuse large B-cell lymphoma (DLBCL) aged <29 years who achieved event-free survival at 24 months (EFS24) compared with an age- and sex-matched general population (online only). (B) OS for patients with DLBCL aged 30–39 years who achieved EFS24 compared with an age- and sex-matched general population (online only). (C) OS for patients with DLBCL aged 40–49 years who achieved EFS24 compared with an age- and sex-matched general population. (D) OS for patients aged 50–59 years who achieved EFS24 compared with the matched general population. (E) OS for patients aged 60–69 years who achieved EFS24 compared with the matched general population. (F) OS for patients aged 70–79 years who achieved EFS24 compared with the matched general population. (G) OS for patients age >80 years who achieved EFS24 compared with the matched general population.

**Table SI.** Demographic and clinical characteristics.

**Table SII.** Cox regression for different risk factors according to International Prognostic Index (IPI).

**Table SIII.** (A) Survival probabilities for overall survival by event-free survival (EFS)  $\geq$ 24 months and age <60 years compared to the standard population. (B) Survival probabilities for overall survival by EFS  $\geq$ 24 months and age  $\geq$ 60 years compared to the standard population.

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