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Event-free survival at 36 months is a suitable endpoint for diffuse large B-cell lymphoma patients treated with immunochemotherapy: real-world evidence from the North Japan Hematology Study Group

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Title

Event-free survival at 36 months is a suitable endpoint for diffuse large B-cell lymphoma patients treated with immunochemotherapy: real-world evidence from the North Japan Hematology Study Group

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Author's Contributions

KI and HG conceived and designed the study, analyzed data and wrote the manuscript. KI, HG, SH, H.Senjo, KS, JH, RO, TS, T.Igarashi, KW, IK, YT, KY, AS, MT, KF, YH, TN, H.Sakai, YK, and MK collected the clinical data. KI, T.Inao, and IY performed all statistical analyses and generated figures and tables. TT developed the methodology and supervised the study. All authors participated in discussions and interpretation of the data and results.

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Running Heads

EFS36 in Asian DLBCL

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Data Sharing Statement

Any requests for study data and protocol will be reviewed by NJHSG. Only requests that have a methodologically sound basis and whose proposed use of the data has been approved by the applicable ethics committees and regulatory authorities will be considered.

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[Abstract]

Information regarding follow-up duration after treatment for newly diagnosed diffuse large B-cell lymphoma (DLBCL) is important. However, a clear endpoint has yet to be established. We totally enrolled 2182 patients newly diagnosed with DLBCL between 2008 and 2018. The median age of the patients was 71 years. All patients were treated with rituximab- and anthracycline-based chemotherapies. Each overall survival (OS) was compared with the age- and sex-matched Japanese general population (GP) data. At a median follow-up of 3.4 years, 985 patients experienced an event and 657 patients died. Patients who achieved an event-free survival (EFS) at 36 months (EFS36) had an OS equivalent to that of the matched GP (standard mortality ratio [SMR], 1.17; P=0.1324), whereas those who achieved an EFS24 did not have an OS comparable to that of the matched GP (SMR, 1.26; P=0.0095). Subgroup analysis revealed that relatively old patients (>60 years), male patients, those with limited-stage disease, those with a good performance status, and those with low levels of soluble interleukin 2 receptor already had a comparable life expectancy to the matched GP at an EFS24. In contrast, relatively young patients had a shorter life expectancy than matched GP, even with an EFS36. In conclusion, an EFS36 was shown to be a more suitable endpoint for newly diagnosed DLBCL patients than an EFS24. Of note, younger patients require a longer EFS period than older patients in order to obtain an equivalent life expectancy to the matched GP.

[Introduction]

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma,[1,2] and chemotherapy combined with rituximab (immunochemotherapy [ICT]), commonly R-CHOP therapy, has dramatically improved the prognosis of DLBCL patients compared to the pre-rituximab era. However, there is still great heterogeneity in their survival, and approximately 30%-40% of patients cannot be cured with first-line therapy, even in the rituximab era.[3-5]

Overall survival (OS) is the definitive efficacy endpoint to evaluate chemotherapy for DLBCL; however, it generally requires a prolonged follow-up period, and a clear endpoint for the follow-up period has not yet been determined. Maurer et al.[6] showed that patients with DLBCL had a significantly decreased survival at diagnosis compared with the age- and sex-matched general population (GP) of their own country (United States and France), and patients who achieved event-free survival (EFS) at 24 months after diagnosis (EFS24) had an OS equivalent to that of the GP. They proposed that EFS24 is useful in patient counseling and should be considered as an endpoint for studies of newly diagnosed DLBCL.

However, while several research groups have attempted similar analyses to validate the conclusions of Maurer et al., the results have been inconsistent.[6-12]

Based on these findings, we assessed whether the prognosis of DLBCL patients who achieved EFS24 was comparable to that of an Asian GP matched for age and sex.

[Methods]

Study design and patient characteristics

The North Japan Hematology Study Group conducted a retrospective population-based cohort study, which included 14 institutes, representing each region in Hokkaido Prefecture, Japan. Newly diagnosed DLBCL patients who were treated with rituximab and anthracycline-based ICT as their initial therapy with curative intent between 2008 and 2018 and who were ≥18 years old at the initial therapy were included. According to the World Health Organization classification,[13, 14] a diagnosis was made by skilled pathologists at each institution. Patients with double-hit lymphoma, primary DLBCL of the central nervous system, T-cell/histiocyte-rich large B-cell lymphoma, primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, or transformed lymphomas were excluded from this analysis. Informed consent was obtained using the opt-out method. This protocol was approved by the institutional review boards of Aiiku Hospital and each participating hospital, and was conducted in accordance with the Declaration of Helsinki.

Outcome definitions

EFS was defined as the time from initial ICT until relapse or progression, unplanned retreatment of lymphoma after initial ICT, death from any cause, or the last follow-up. EFS indicators at predefined cut-off points (i.e., EFS at 12 months [EFS12], 24 months [EFS24], 36 months [EFS36], or 48 months [EFS48]) were defined based on the EFS at the indicated cut-off point after the date of initial therapy. For all patients, the OS was defined as the time from initial ICT to death from any cause or the last follow-up, and for patients achieving EFS12, EFS24, EFS36, and EFS48, it was defined as the time from each EFS milestone to

death from any cause or the last follow-up. The causes of death were divided into three groups: progressive or refractory disease that did not respond to treatment, complications from aggressive chemotherapy, and other reasons unrelated to lymphoma.

Statistical methods

Because normal values for lactate dehydrogenase (LDH) and soluble interleukin 2 receptor (sIL-2R) vary by facility, the values divided by the upper limit of normal (LDH and sIL-2R ratios) were used for these variables. Patient survival rates were calculated using the Kaplan-Meier method.[15] The OS of patients were compared with those of age-, sex-, and calendar-period-matched Japanese GP. The expected survival curve was created using data on mortality in the GP obtained from Vital Statistics supplied by the Japanese Ministry of Health, Labour, and Welfare.[16] Standardized mortality ratios (SMRs)[17] and 95% Poisson's confidence intervals (CIs) were calculated. Event- and death-specific cumulative incidences were calculated using a competing risk approach.[18] Subgroup analyses were conducted using threshold values for clinical factors determined by time-dependent receiver operating characteristic (ROC) curves[19] at 36 months after initial ICT (36-month EFS-ROC analysis). Analyses to calculate the SMR were implemented using proc stdrate in the SAS software program (version 9.4; SAS Institute, Cary, NC, USA). Other analyses were performed using the R software (version 2.14; R Foundation for Statistical Computing, Vienna, Austria).

[Results]

Patients' characteristics and survival outcomes

A total of 2182 patients with newly diagnosed DLBCL treated with ICT were enrolled in the study. The median patient age was 71 years (range, 19–99 years), and 53% of the patients were male. The percentages of patients with advanced-stage disease and lymphomatous involvement in NCCN-IPI-defined high-risk extranodal organs (NCCN-ENs; bone marrow, central nervous system, Liver, gastrointestinal tract, or lung)[20] were 59% and 40%, respectively. Seventy-nine percent and 62% of patients had elevated levels of sIL-2R, and LDH, respectively. Since the cell of origin (COO)[21] was not assessed in 37.4% of the patients and the degree of bias was considered to be significant, we did not analyze survival using COO in the current study (Table 1).

All patients were treated with rituximab- and anthracycline-based chemotherapies. Ninety-seven percent of patients were treated with R-CHOP and its variants. Upfront autologous hematopoietic stem cell transplantation following high-dose chemotherapy was performed in 1.1% of patients. At a median follow-up of 3.5 years, 985 patients (45%) had an event and 657 patients (30%) had died. The percentages of estimated survival for EFS12, EFS24, EFS36, EFS48, and EFS60 were 72.9%, 64.4%, 60.2%, 55.8%, and 53.3%, respectively (Figure S1A). The percentages of estimated OS at 12, 24, 36, 48, and 60 months from initial ICT were 86.8%, 79.0%, 75.1%, 71,8%, and 69.0%, respectively (Figure S1B).

The comparison of survival rates between the patients and the GP along with the validation of the EFS24

At the induction of ICT, patients had a significantly decreased survival compared with the age- and sex-matched GP, with an SMR of 3.10 (95% CI 2.87-3.35; Figure 1A). Although the survival improved as patients remained in a disease-free state, the SMR was still significant when patients achieved EFS12 (SMR 1.50; 95% CI 1.31 to 1.71; Figure 1B) and EFS24 (SMR 1.26; 95% CI 1.06-1.48; Figure 1C). Patients who achieved an EFS36 had an OS equivalent to that of the matched GP (SMR 1.17; 95% CI 0.95-1.43; Figure 1D).

Loss of residual lifetime estimation

We estimated the loss of residual lifetime in patients with each prognostic factor using SMR. The threshold values for each variable were determined by the Youden index using a 36-month EFS-ROC analysis[18](Figure S2A-D). The threshold for an age factor of 60 years was determined based on previous reports.[20, 22, 23] At the time of ICT induction, patients with unfavorable prognostic factors defined by the NCCN-IPI other than age (advanced stage, poor performance status, NCCN-EN, and high LDH ratio) had a poorer SMR than those with favorable prognostic factors (Figure 2A). These differences in SMR decreased with continued disease-free status (Figure 2B-D). Regarding the clinical stage and performance status, at EFS36, a significant difference in residual lifetime between GP and patients with favorable prognostic factors was no longer present; however, the difference persisted in patients with unfavorable prognostic factors (Figure 2C). For the LDH ratio and extranodal disease, the disadvantage in residual lifetime compared to GP disappeared in both patients with favorable and unfavorable prognostic factors after achieving an EFS36 (Figure 2C). At the time of ICT implementation, women tended to have a worse SMR than men, and

relatively young patients (≤60 years) had a worse SMR than older patients (>60 years) (Figure 2A). The significant difference in residual lifetime between DLBCL patients and GP was eliminated in men and older patients at the achievement of EFS24 (Figure 2B). However, in women and younger patients, the difference was present at EFS36 (Figure 2C) but was eliminated when EFS48 was achieved (Figure 2D).

Next, we evaluated the loss of residual lifetime in the patients with high sIL-2R levels. With the introduction of ICT, patients with high sIL-2R ratios had worse SMR than those with low sIL-2R ratios (Figure 2A). At the time of achieving an EFS36, the disadvantage in residual lifetime compared to the GP disappeared in patients with a low sIL-2R ratio, but not in those with a high sIL-2R ratio (Figure 2C). At EFS48, significant differences in SMR in all subgroups disappeared (Figure 2D).

Events decomposition

Events from each EFS milestone were evaluated in detail. At the time of induction therapy, the 5-year cumulative incidences of DLBCL relapse, treatment-related death, unplanned consolidative therapy, DLBCL-related death, and death due to other causes were 26.4% (95% CI, 24.4%-28.5%), 2.9% (95% CI, 2.2%-3.6%), 9.9% (95% CI, 8.7%-11.3%), 3.5% (95% CI, 2.7%-4.3%), and 4.0% (95% CI, 3.2%-5.0%), respectively (Figure 3A). The cumulative incidence of DLBCL relapse decreased as patients remained in the disease-free state, but still accounted for the majority of future events at each EFS milestone (5-year cumulative incidences from EFS12, EFS24, and EFS36 were 21.9%, 17.2%, and 14.5%, respectively). Death due to other causes was the second most common future event, and its

cumulative incidence was similar at EFS12, EFS24, and EFS36 (5-year cumulative incidences at EFS12, EFS24, and EFS36 were 6.6%, 6.9%, and 7.0%, respectively). The future risks of the other event types at EFS12, EFS24, and EFS36 were very low (Figure 3B-D).

Description of death

The causes of death from each EFS milestone were evaluated. At the time of induction therapy, the 5-year cumulative incidences of DLBCL-related death, treatment-related death, and death due to other causes were 21.2% (95% CI, 19.3%–23.1%), 4.3% (95% CI, 3.5%–5.3%), and 5.4% (95% CI, 4.4%–6.6%), respectively (Figure 4A). However, the cumulative incidence of DLBCL-related death decreased as patients remained disease-free (5-year cumulative incidences at EFS12, EFS24, and EFS36 were 8.1%, 5.1%, and 3.2%, respectively). The cumulative risk of death due to other causes was similar at EFS12, EFS24, and EFS36 (5-year cumulative incidences were 8.0%, 7.6%, and 8.1%, respectively), ultimately becoming the most common cause of death (Figure 4B-D).

[Discussion]

This study is the first validation in Asia and one of the largest comparisons of survival between patients with newly diagnosed DLBCL and GP. We confirmed that DLBCL patients treated with ICT who remained event-free for three years had an equivalent survival compared to the GP matched for age, sex, and calendar period, and concluded that the future outcomes of patients surviving without events 2 years after ICT may be clinically

indistinguishable, but marginally worse than those of the matched GP in terms of survival. We also showed that the event-free period required to achieve a life expectancy comparable to that of the GP varies by subgroup. Since the population of Hokkaido Prefecture accounts for approximately 4% of the total Japanese population[24], and the participating institutions in this study are flagship hospitals representing each region of Hokkaido, our cohort is therefore considered to be representative of the entire DLBCL cohort in Japan.

Several similar studies[6-12] comparing the prognosis of newly diagnosed DLBCL patients and GP have been conducted in the past from different regions and countries; however, the findings were not always consistent. Maurer et al.[6] showed that the OS of DLBCL patients who achieved EFS24 was comparable to that of GPs matched for age and sex in the United States and France. An analysis by Denmark[8] reported that the subsequent survival of DLBCL patients who achieved event-free survival 24 months after the end of treatment was still worse than that of the GP. This report[8] differs from that of Maurer et al.'s study[6] in two ways: first, the milestone of event-free survival was defined from the end of treatment rather than from the diagnosis, and second, unplanned treatment of lymphoma after initial immunochemotherapy was not considered an event. These differences may account for the differences in results.

In the present study, we adopted the approach of Maurer et al.[6] and defined each milestone as starting from the time of the therapeutic intervention and incorporating unexpected therapeutic interventions as events; however, the survival rate of patients who achieved an EFS24 was still lower than that of the GP. Interestingly, we revealed that patients with DLBCL had similar survival rates to their age- and sex-matched counterparts in the GP

after achieving EFS36 instead of EFS24. This discrepancy may be due to the inclusion of more patients of older age or with a worse performance status in comparison to the previous study,[6] which may have reduced the actual treatment intensity and decreased survival rates after achieving an EFS24. Another possible explanation is that life expectancy in Japan (84.3 years) is generally longer than in Western countries (78.5 years in the United States and 82.5 years in France),[25]Japanese DLBCL patients who achieve an EFS24 may be at a disadvantage in comparison to their Western counterparts in achieving a prognosis comparable to that of the GP.

On the other hand, a study comparing the subsequent prognosis of patients achieving a progression-free survival at 24 months (PFS24) with the GP in a Japanese cohort was recently reported[12]. Although the SMR (1.29) values in this report were similar to ours (1.26), they concluded that patients who achieved PFS24 had no excess mortality compared to matched GP, which is opposite to our conclusion. This may be partly because the study design of this report (e.g., clinical trial, unscheduled lymphoma treatment after initial immunochemotherapy not considered an event) differs from our report (e.g., including older, poor performance status, or inadequately treated patients), and partly because the number of patients achieving PFS24 (334 patients) is smaller than that of patients achieving EFS24 in our report (1241 patients, Figure 1C), resulting in a wider CI range.

Our subgroup analysis revealed different prognoses in different categories. Male patients or >60 years of age were able to attain a life expectancy similar to the GP at each milestone beyond EFS24. However, the disadvantages in the remaining life expectancy for female patients or those aged 60 and below only disappeared upon reaching EFS48. These

results imply that younger patients and female patients require a longer EFS period than older patients and male patients, respectively, in order to obtain an equivalent life expectancy to the matched GP. This is thought to be because the life expectancy of the compared GP was longer in younger patients than in older patients. The same reason may also explain why women require a longer EFS than men do to obtain a life expectancy equivalent to that of the matched GP.

One of the strong messages from this paper is that, in the sense of losing more of the expected remaining lifespan, young age is considered a poor prognostic factor in the context of newly diagnosed DLBCL. However, it should be noted that there are differences of opinion on this matter in previous papers. In a similar sub-analysis figure in Maurer's report,[6] which focused on cases in the United States and France, it seems that younger patients (≤60 years old) have a higher SMR compared to older patients (>60 years old). On the other hand, a report from Denmark[8] concluded that patients aged <50 years quickly normalized to the GP, whereas patients aged ≥50 years had continuously increased mortality. Furthermore, a report from Sweden[11] also stated that patients aged <60 years had an OS comparable to the standard population after the achievement of the EFS24 milestone. There is no clear answer for the differing conclusions, but one possible explanation could be the involvement of factors such as the race of the study subjects or the research design. In the latter two reports,[8, 11] differences between our report and Maurer et al.'s report[6] include the limitation of the study subjects to those who achieved complete remission and not considering unexpected retreatments performed after the initial ICT as events.

The present study suggests that EFS36 is a reasonable goal for DLBCL in clinical

practice, but also that different subgroups may have different target EFS durations. Based on the results of this study, we are currently developing a system for calculating the appropriate EFS attainment period for each patient to provide patients with information about the target event-free period required to achieve a residual life expectancy equivalent to that of the age- and sex-matched GP. We expect the use of this new system in conjunction with traditional prognostic systems (e.g., the IPI,[22] R-IPI,[23] and NCCN-IPI[20]) to provide patients with enhanced prognostic information.

Maurer et al.[6] demonstrated that DLBCL relapse was the most common 5-year cumulative event from the time of diagnosis (5-year cumulative incidence:30%) and EFS12 (13%), and that the risk of future DLBCL relapse at EFS24 (8%) was the same as the risk of death due to unrelated causes. In contrast, DLBCL relapse was consistently the most common future event among all of the EFS milestones in the current study (5-year cumulative incidences from ICT induction, EFS12, EFS24, and EFS36 were 26.4%, 21.9%, 17,2%, and 14.5%, respectively). On the other hand, a study focusing on late recurrence in an Asian population-based cohort was reported from South Korea.[26] In their cohort, among 169 of 846 (20%) DLBCL patients who achieved complete remission (CR) upon first-line R-CHOP experienced a relapse; 51 (30.2%) experienced a late relapse (defined as disease recurrence at least 2 years after the confirmation of CR). In our cohort, 430 of 1649 (26.1%) DLBCL patients who achieved a CR experienced a relapse, with 170 (39.5%) and 43 (10.0%) of these patients experiencing a relapse at least 2- and 5-years after ICT, respectively (data not shown). The Korean report[26] and ours are similar in that they both analyzed Asian population-based cohorts, but our cohort appears to have a higher late

recurrence rate. Two reasons can be postulated as to why the risk of DLBCL recurrence was higher in this study than in the previous studies.[6, 26] First, there is a possibility that some of the patients may have received less intensive chemotherapy than others[6,26] due to older age (the median age of the patients in the United States, Korean, and our datasets are 63, 57, and 71 years, respectively) or poor performance status (the percentage of patients with performance status greater than 1 in the United States, Korean, and our datasets are 19, 5.1, and 26%, respectively), leading to both early and late relapses following treatment, as previously mentioned. Based on this possibility, we conducted an additional investigation into the 5-year cumulative recurrence rate of DLBCL in patients who achieved EFS24, categorizing them into three groups based on age at ICT: young (less than 60 years of age), intermediate (between 61 and 80 years of age), and elderly (81 years of age and older). The 5-year cumulative recurrence rates of the good and poor PS groups were 10.3% and 14.3%, respectively, in the young group, 15.8% and 31.0% in the intermediate group, and 14.1% and 28.8% in the elderly group (Figure S3A-C). In the two groups other than the young group, the intensity of ICT, potentially adjusted according to the PS, might have influenced the rate of recurrence after achieving EFS24. On the other hand, in the group of younger patients, there was no apparent difference in the 5-year cumulative DLBCL recurrence rate between the good and poor PS groups. This suggests that, even with a poor PS, it is possible that treatment with a certain level of intensity was maintained in younger patients who could achieve an EFS24. Second, it is possible that the relapsed cases included those who relapsed as DLBCL and indolent lymphoma.[27] Patients with DLBCL who transformed from indolent lymphoma were excluded from the study, but no pathologic data were

available at the time of lymphoma recurrence. While Maurer et al.'s report[6] distinguished between recurrence as DLBCL and recurrence as low-grade lymphoma, the current report could not make these distinctions, so the actual number of recurrences as DLBCL might have been relatively low.

DLBCL-related death was the most common risk factor for future mortality at ICT induction; however, this risk decreased as the patients continued in a disease-free state, and DLBCL non-associated death became the most common risk factor. The 5-year cumulative DLBCL-related mortality rate for patients achieving EFS36 was only 3.2%, suggesting that EFS36 is an appropriate goal for DLBCL in practice and may be an appropriate endpoint for DLBCL clinical studies.

Several limitations of the present study warrant mention. In this study, the actual dose of chemotherapeutic drugs administered to each patient was unclear. Some of the patients in this study were very old or in poor general condition but were administered curative chemotherapy to meet the wishes of the patients and their families from a practical perspective. Because induction therapy was interrupted in some of these cases due to treatment toxicity, the actual survival outcome of patients who received adequate dosing is unknown. Additionally, this study lacked pathological data at the time of lymphoma recurrence. As the survival rate of patients with recurrent DLBCL is worse than that of patients with low-grade recurrence, a biopsy at recurrence is, in principle, mandatory for diagnosis.[28] However, it was not possible to perform a biopsy in all patients with recurrence because of the retrospective nature of the study. Even if possible, discrepancies in the results due to the biopsy sites cannot always be ruled out. Furthermore, the use of novel

agents such as polatuzumab vedotin as first-line therapy for DLBCL[29] may yield results that differ from those of the present study. Additionally, the details of the treatment administered at the time of recurrence were not available in this study. After achieving EFS24 and EFS36, patients of 60 years of age and younger had disadvantages in remaining life expectancy in comparison to the GP. Among these patients, DLBCL relapse was the most common future event (5-year cumulative incidence:14.1%; Figure S4A), and DLBCL-related death was the most common risk factor for future mortality (5-year cumulative incidence:4.2%; Figure S4B). In the future, in conjunction with high-dose chemotherapy followed by autologous stem cell transplantation, which remains a promising treatment option[30], the prognosis for these younger patients with the relapsed disease may be improved by the use of novel agents such as polatuzumab vedotin[31], chimeric antigen receptor T-cell therapy (CAR-T)[32-35], and bispecific T-cell engager therapy[36]. Further studies are needed to address this issue.

In conclusion, validation of a large cohort of Asian patients revealed that DLBCL patients can have a prognosis comparable to that of the GP matched by age and sex when they achieve EFS36 in actual practice instead of EFS24. It is also clear that the target EFS differs according to various factors, and a more individualized prognostic system needs to be developed. As discrepant results may be obtained due to differences in life expectancy, population age distribution, and healthcare systems among countries, verification in other countries and regions is also needed.

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Table 1.

Factors		n	%
Age, years	median (range)	71 (19-99)	
	≤40	76	3.5%
	41-60	417	19.1%
	61-75	956	43.8%
	≥76	733	33.6%
Sex	Male	1159	53.1%
	Female	1023	46.9%
PS	≥2	568	26%
CS	≥3	1287	59%
LDH	>ULN	1346	61.7%
NCCN-EN	present	882	40.4%
sIL-2R	WNL	445	20.6%
	ULN – 1.5 × ULN	279	12.9%
	>1.5 × ULN	1437	66.5%
IPI	Low	618	28.3%
	Low-intermediate	468	21.4%
	High-intermediate	497	22.8%

	High	599	27.5%
COO	**GCB**	715	32.8%
	non-GCB	650	29.8%
	NA	817	37.4%

Table 1: Patients' characteristics (n = 2182)

Abbreviations: PS, Eastern Cooperative Oncology Group performance status; CS, clinical stage; LDH, lactate dehydrogenase; NCCN-EN, National Comprehensive Cancer Network - international prognostic index defined high-risk extranodal disease (bone marrow, central nervous system, gastrointestinal tract, liver, lung); sIL-2R, soluble interleukin 2 receptor; IPI, International Prognostic Index; COO, cell of origin; GCB, germinal center B-cell-like type; WNL, within normal limits; ULN, upper limit of normal; NA, not assessed.

Figure Legend

Figure 1. Overall survival of diffuse large B-cell lymphoma versus the expected survival.

(A) The overall survival since induction of immunochemotherapy; (B) the overall survival since the event-free survival at 12 months evaluation; (C) the overall survival since the event-free survival at 24 months evaluation; (D) the overall survival since the event-free survival at 36 months evaluation. DLBCL, diffuse large B-cell lymphoma; SMR, standardized mortality ratio; CI, confidence intervals.

Figure 2. Forest plots of the standardized mortality ratio in diffuse large B-cell lymphoma subgroups.

Forest plots of the standardized mortality ratio in diffuse large B-cell lymphoma subgroups for (A) all patients and patients who achieved an event-free survival for (B) 24 (EFS24), (C) 36 (EFS36), and (D) 48 (EFS48) months. Horizontal bars indicate 95% confidence intervals.

CS, clinical stage; PS, performance status; sIL-2R, soluble interleukin 2 receptor; LDH, lactate dehydrogenase; NCCN-EN, National Comprehensive Cancer Network - international prognostic index defined high-risk extranodal disease (bone marrow, central nervous system, gastrointestinal tract, liver, lung).

Figure 3. Event-specific cumulative incidences based on a competing risk analysis.

Event-specific cumulative incidences based on a competing risk analysis for (A) all patients at initial immunochemotherapy; (B) patients achieving an event-free survival for 12 months (EFS12); (C) patients achieving an EFS24; and (D) patients achieving an EFS36. DLBCL, diffuse large B-cell lymphoma.

Figure 4. Death-specific cumulative incidences based on a competing risk analysis.

Death-specific cumulative incidences based on a competing risk analysis for (A) all patients at initial immunochemotherapy; (B) patients achieving event-free status for 12 months (EFS12); (C) patients achieving an EFS24; and (D) patients achieving an EFS36. DLBCL, diffuse large B-cell lymphoma.

Figure 1

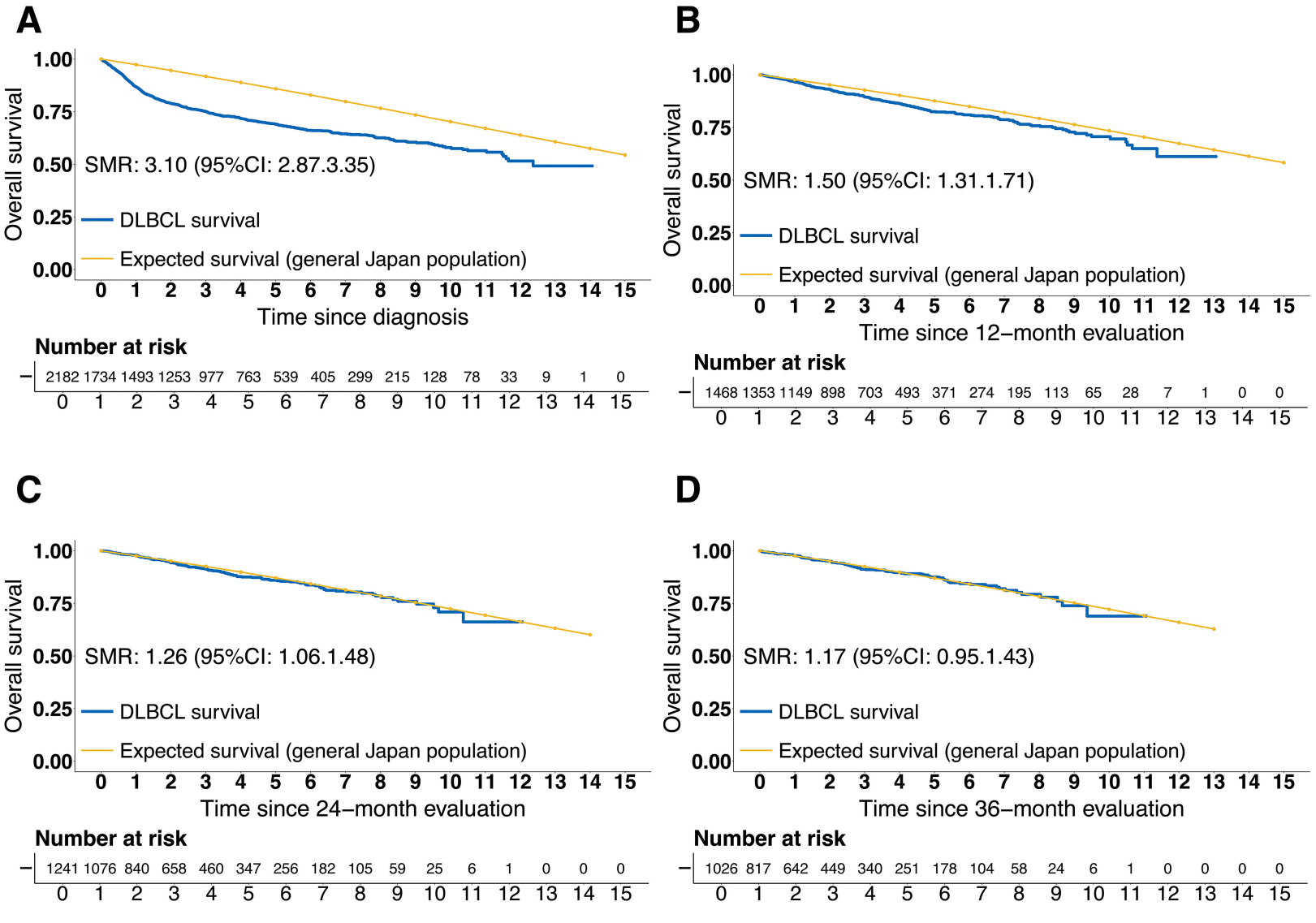

A
Overall survival
1.00
0.75
0.50
0.25
0.00
SMR: 3.10 (95%CI: 2.87.3.35)
DLBCL survival
Expected survival (general Japan population)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since diagnosis
Number at risk
2182 1734 1493 1253 977 763 539 405 299 215 128 78 33 9 1 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
B
Overall survival
1.00
0.75
0.50
0.25
0.00
SMR: 1.50 (95%CI: 1.31.1.71)
DLBCL survival
Expected survival (general Japan population)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since 12−month evaluation
Number at risk
1468 1353 1149 898 703 493 371 274 195 113 65 28 7 1 0 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
C
Overall survival
1.00
0.75
0.50
0.25
0.00
SMR: 1.26 (95%CI: 1.06.1.48)
DLBCL survival
Expected survival (general Japan population)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since 24−month evaluation
Number at risk
1241 1076 840 658 460 347 256 182 105 59 25 6 1 0 0 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
D
Overall survival
1.00
0.75
0.50
0.25
0.00
SMR: 1.17 (95%CI: 0.95.1.43)
DLBCL survival
Expected survival (general Japan population)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since 36−month evaluation
Number at risk
1026 817 642 449 340 251 178 104 58 24 6 1 0 0 0 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Figure 2

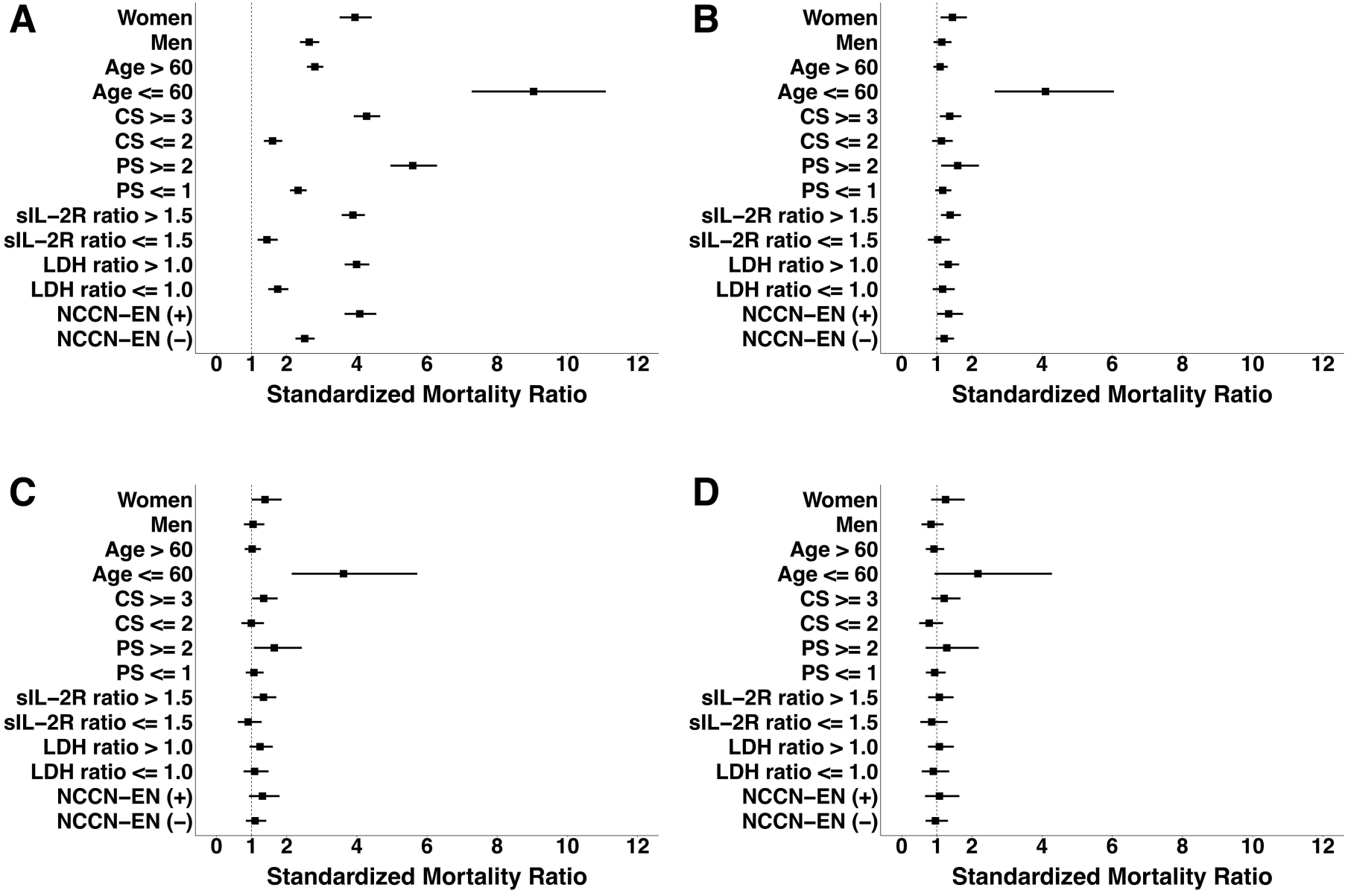

A
Women
Men
Age > 60
Age <= 60
CS >= 3
CS <= 2
PS >= 2
PS <= 1
sIL−2R ratio > 1.5
sIL−2R ratio <= 1.5
LDH ratio > 1.0
LDH ratio <= 1.0
NCCN−EN (+)
NCCN−EN (−)
0 1 2 4 6 8 10 12
Standardized Mortality Ratio
B
Women
Men
Age > 60
Age <= 60
CS >= 3
CS <= 2
PS >= 2
PS <= 1
sIL−2R ratio > 1.5
sIL−2R ratio <= 1.5
LDH ratio > 1.0
LDH ratio <= 1.0
NCCN−EN (+)
NCCN−EN (−)
0 1 2 4 6 8 10 12
Standardized Mortality Ratio
C
Women
Men
Age > 60
Age <= 60
CS >= 3
CS <= 2
PS >= 2
PS <= 1
sIL−2R ratio > 1.5
sIL−2R ratio <= 1.5
LDH ratio > 1.0
LDH ratio <= 1.0
NCCN−EN (+)
NCCN−EN (−)
0 1 2 4 6 8 10 12
Standardized Mortality Ratio
D
Women
Men
Age > 60
Age <= 60
CS >= 3
CS <= 2
PS >= 2
PS <= 1
sIL−2R ratio > 1.5
sIL−2R ratio <= 1.5
LDH ratio > 1.0
LDH ratio <= 1.0
NCCN−EN (+)
NCCN−EN (−)
0 1 2 4 6 8 10 12
Standardized Mortality Ratio

Figure 3

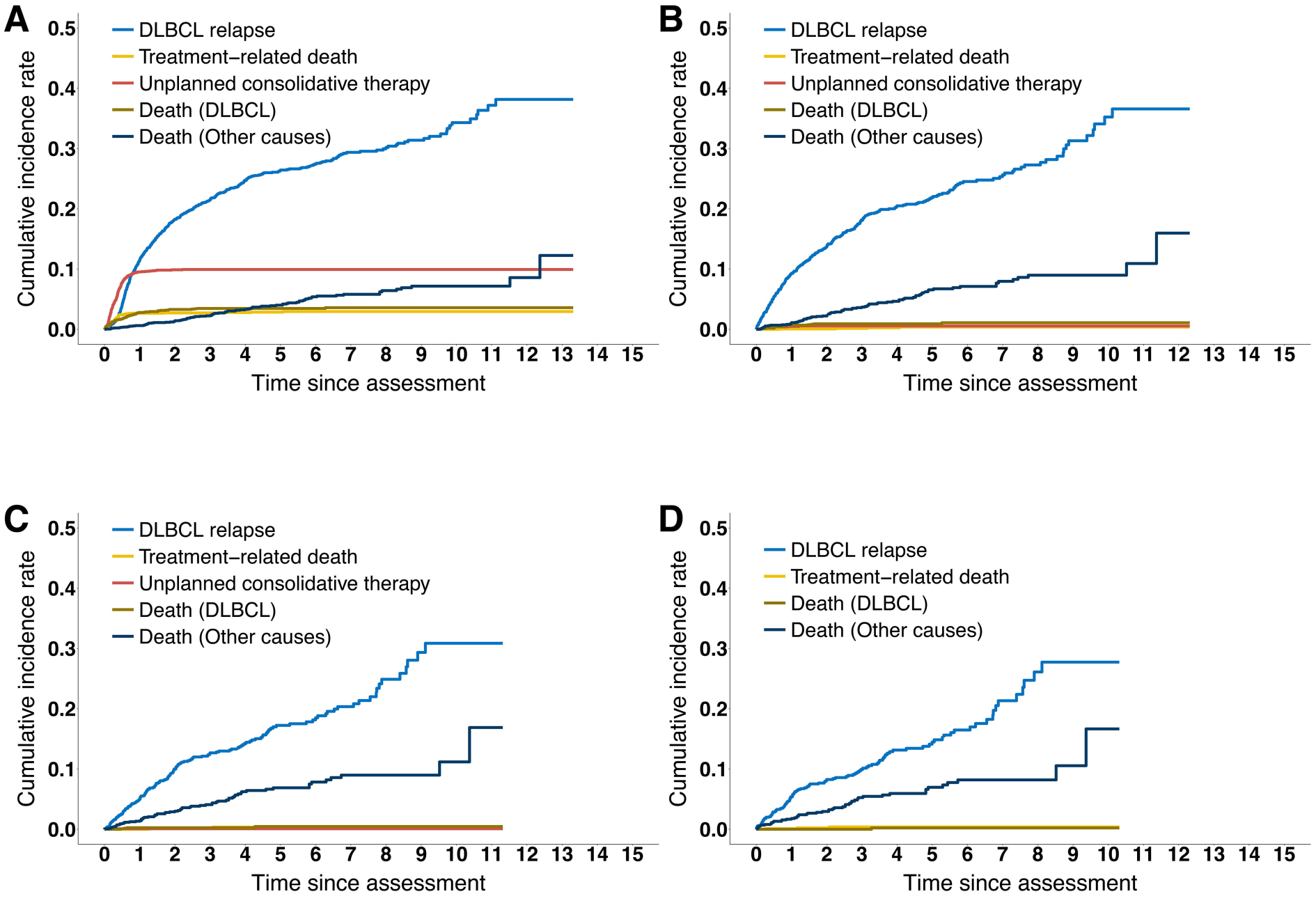
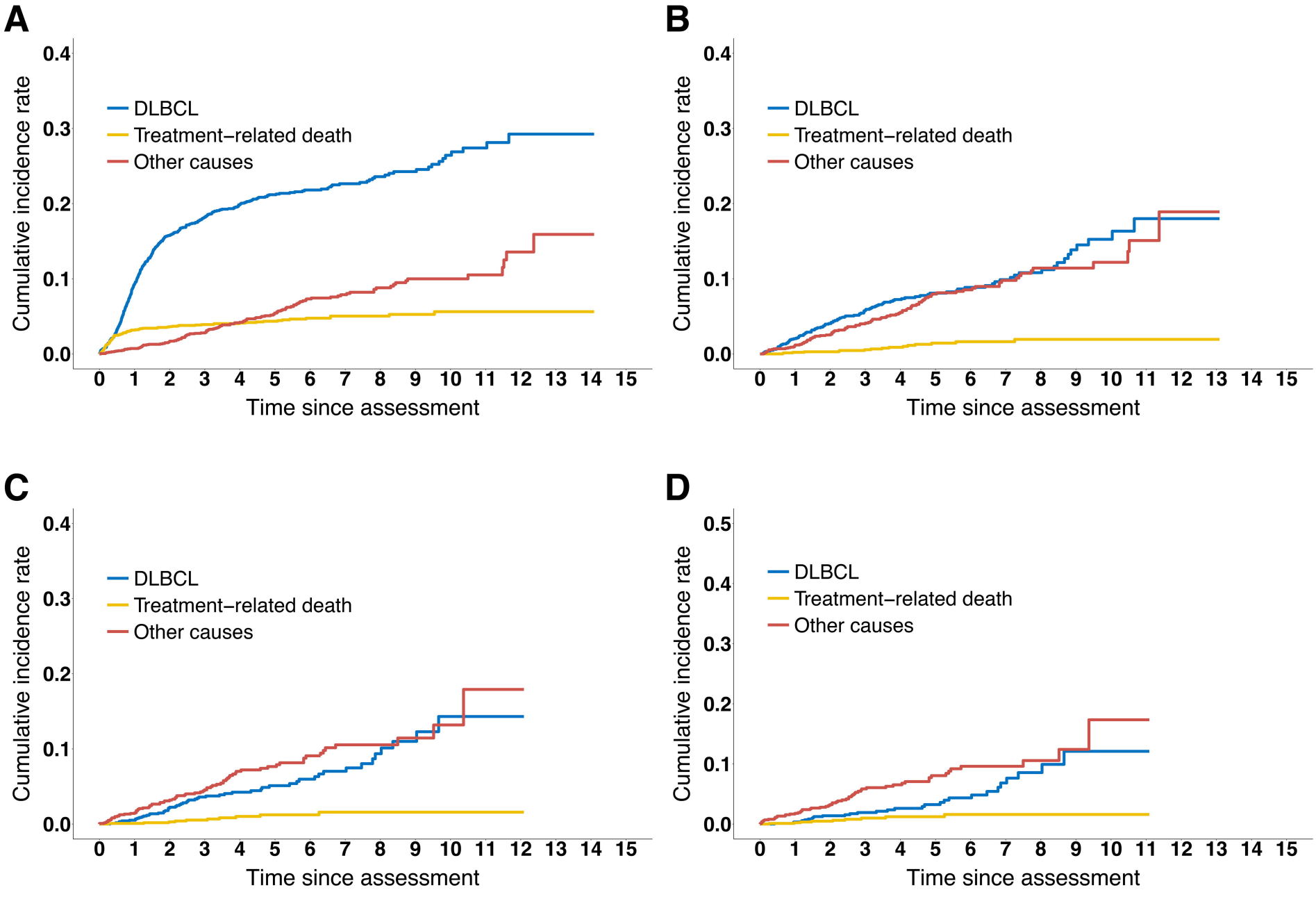

A
B
C
D
DLBCL relapse
Treatment−related death
Unplanned consolidative therapy
Death (DLBCL)
Death (Other causes)
Cumulative incidence rate
0.0
0.1
0.2
0.3
0.4
0.5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since assessment

Figure 4


A
B
C
D
Cumulative incidence rate
Time since assessment
DLBCL
Treatment−related death
Other causes
0.0
0.1
0.2
0.3
0.4
0.5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Supplemental Figure 1. Kaplan-Meier Survival curves.

(A) Event-free survival and (B) overall survival of all patients after initial immunochemotherapy.

Supplemental Figure 2. ROC curves for clinical factors.

ROC curves for clinical factors ([A] LDH ratio, [B] sIL-2R ratio, [C] clinical stage, and [D] performance status) at 36 months after initial immunochemotherapy. The numbers in the upper left of the figure indicate the threshold values (false positive and true positive rates). The cut-off value, dotted in black, was calculated using the Youden index via the approach of Heagerty et al.[19] Considering clinical use, the thresholds of the LDH and sIL-2R ratios were set at 1.00, and 1.50, respectively (dotted in red). ROC, receiver operating characteristic; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin 2 receptor; AUC, area under the curve.

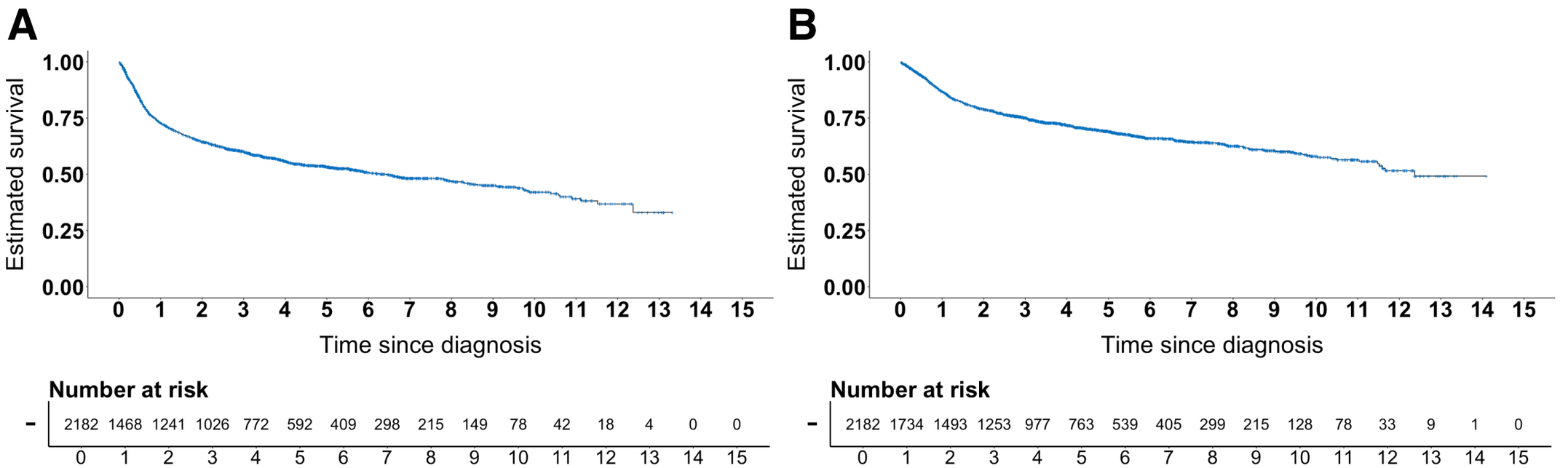
Supplemental Figure 3. Relapse-specific cumulative incidences from event-free status at 24 months based on a competing risk analysis.

Relapse-specific cumulative incidences based on a competing risk analysis for (A) patients under 60 years old; (B) patients between 61 and 80 years old; and (C) patients 81 years of age and older with good or poor performance status. PS, performance status; HR, hazard ratio; CI, confidence intervals.

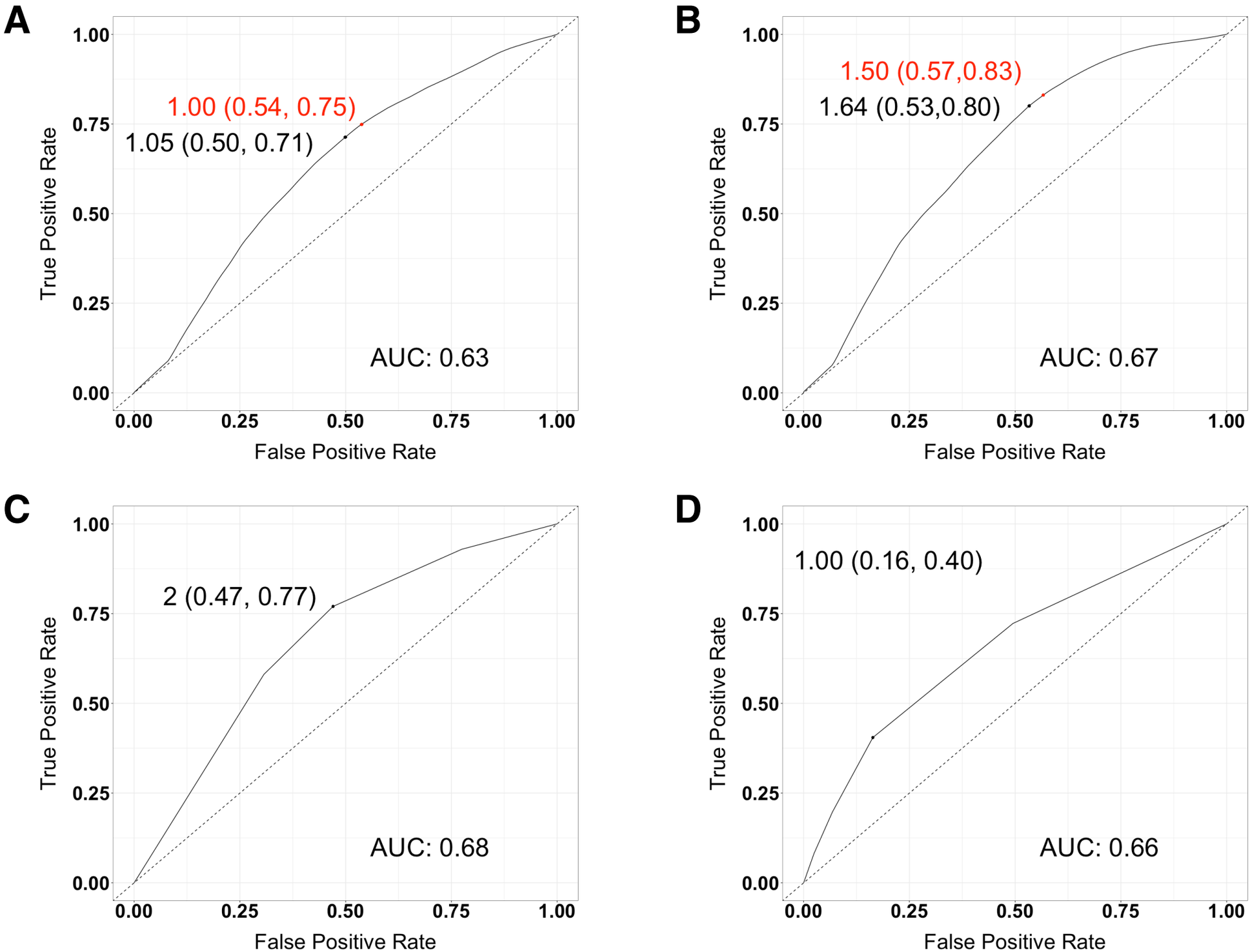
Supplemental Figure 4. Cumulative incidences from event-free status at 24 months of the patients under 60 years old based on a competing risk analysis.

(A) Event-specific cumulative incidences and (B) death-specific cumulative incidences. DLBCL, diffuse large B-cell lymphoma.

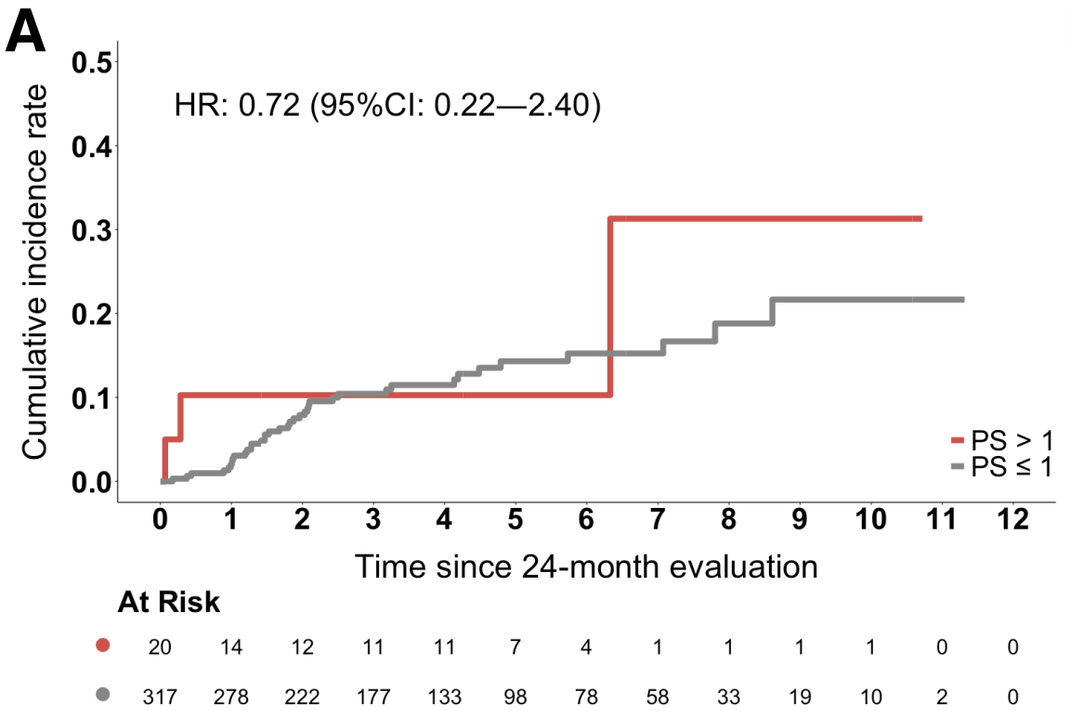
Supplemental Figure 1

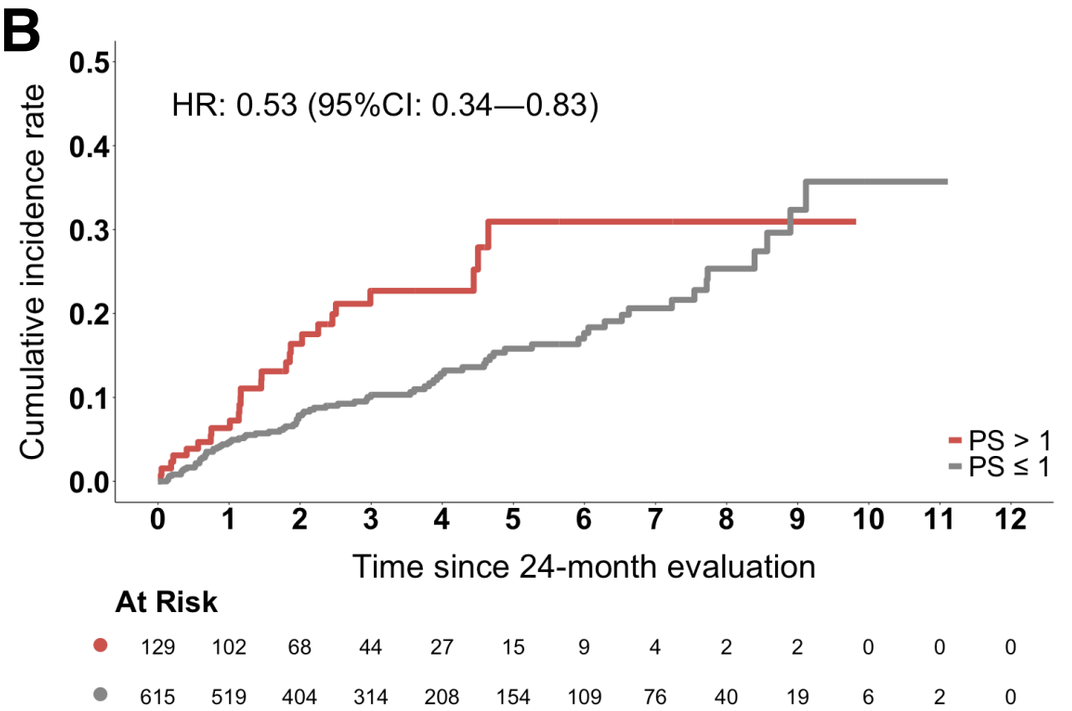


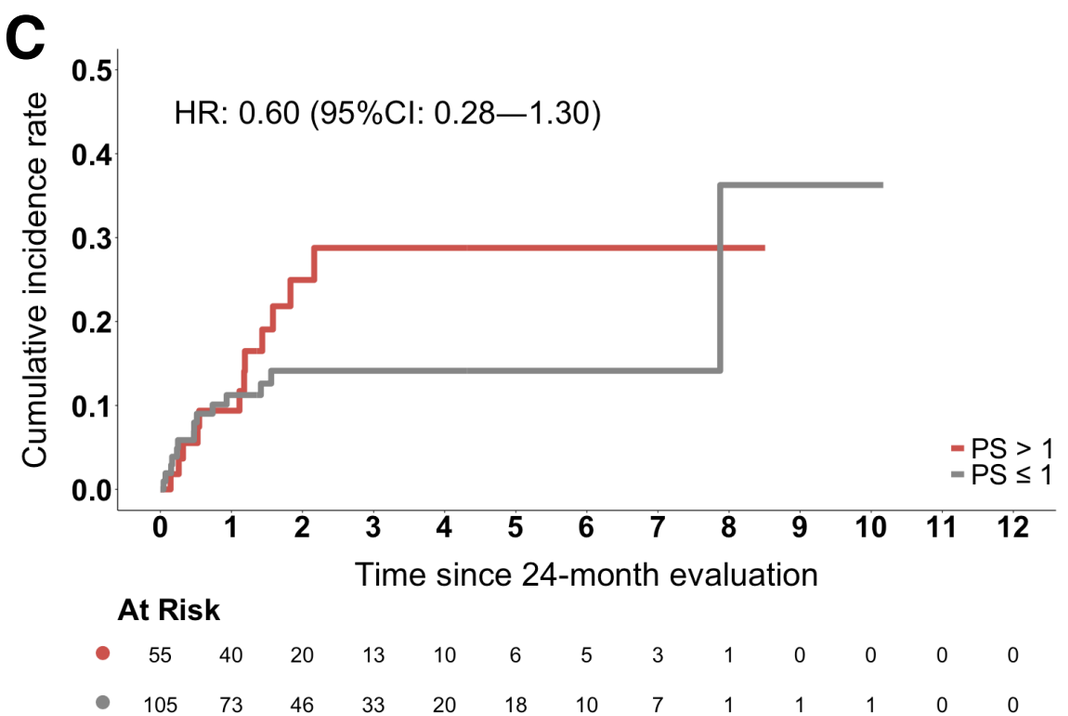
Supplemental Figure 2



Supplemental Figure 3







Supplemental Figure 4