# Link between disease status at 24 months and mortality in follicular lymphoma

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follicular lymphoma, mortality, cause of death, event-free survival, progression of disease, POD24

Although the life expectancy of patients with follicular lymphoma (FL) has improved considerably over the last 20 years (1–4), approximately 20% of patients still experience disease progression (POD) within 24 months of first line therapy.(5,6) This early progression is an established independent risk factor for poor survival.(5–8) In addition, recent studies reported that complete remission at 24 months post diagnosis or 30 months after induction therapy predicts a similar life expectancy to that of the general population.(9,10) This study aimed to evaluate the links between disease status at 24 months, mortality, and causes of death in FL patients.

This retrospective study included patients diagnosed with FL between 1997 and 2016, across nine institutions. After excluding patients with composite histology at diagnosis, FL subclassified as grade 3b, histological transformation before treatment, patients whose survival status or cause of death was unknown, and patients who were lost to follow-up, 990 patients were eligible. Causes of death were classified as either death following progressive lymphoma or other cause. Early progression of disease (POD24) was defined as progression within 24 months of the first-line therapy, while non-POD24 was defined as the absence of relapse, progression, or death due to any cause within 24 months of first-line therapy. Patients whose follow-up was < 24 months but who were event-free, or who died from causes other than progressive lymphoma before 24 months, were not included in either the POD24 or non-POD24-subgroups (Supporting Fig. S1).

Competing risk models were used to estimate the cumulative incidence of death from progressive lymphoma or other causes. Net survival was considered as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer-free individuals. Excess mortality was evaluated using corresponding control populations of similar age and sex; the excess mortality model and the penalized spline approach were used to compute excess mortality.(11,12) Survival rates were calculated using the same technique, which was based on multiple penalized splines. The mortality rates of patients with low-grade FL, from this dataset, were published previously.(13)

The median age at diagnosis was 60 years (range: 17–100 years). Approximately two-thirds of the patients (65.7%) presented with advanced-stage disease, and 51.9% of the patients were women. The most common initial treatment approach was immunochemotherapy (73.3%). Within the 24 months of treatment, 174 patients (17.6%) experienced progression (POD24-patients), while 630 patients (63.6%) did not. Patient characteristics according to the disease status at 24 months are presented in Supporting Table 1.

This cohort had a median follow-up of 67 months (range: 0–226 months) during which time there were 217 deaths, 50.2% of which were the result of lymphoma progression. The estimated 10-year OS, DSS, and net survival rates for this population were 69.8% (95% CI: 66.2–73.0%), 83.8% (95% CI: 80.7–86.4%), and 83.8% (95% CI: 79.8–87.0%), respectively.

In the non-POD24-patient group, excess mortality was observed for at least 10 years, and it did not decrease with time (Fig. 1A). Furthermore, in the non-POD24-patient group, the estimated 10-year net survival was 90.4% (95% CI: 85.3–93.8%); the total and net survival rates are shown in Fig. 1B.

The cumulative incidence of deaths due to progressive lymphoma and deaths due to other causes were similar across the entire study population (Fig. 2A). However, among the non-POD24-patients, the cumulative incidence of deaths due to progressive lymphoma was lower than that of other causes, with an estimated 10-year cumulative incidence of only 7.8% (95% CI: 5.1–10.9%) vs. 12.9% (95% CI: 9.8–16.5%), respectively (Fig. 2B). In contrast, among the POD24-patients, the cumulative incidence of deaths due to progressive lymphoma was higher than that of other causes,

with an estimated 10-year cumulative incidence of 47.3% (95% CI: 38.5%–55.4%) vs. 7.8% (95% CI, 3.8%–12.1%), respectively (Fig. 2C).

In addition, first remission length had an impact on the later course of the disease, as non-POD24-patients had a better DSS than POD24-patients after second-line treatment (Supporting Fig. S2).

In our unselected, real-life population of 990 FL patients, the probability of death due to progressive lymphoma was similar to that of other causes. Deaths from progressive lymphoma were predominant among POD24-patients, similar to findings from previous studies. However, we also observed excess mortality and deaths due to progressive lymphoma among non-POD24-patients. Magnano et al., reported that FL patients whose first remission lasted for at least 30 months had a similar life expectancy to that of the general population.(9) Maurer et al. also reported that there was no subsequent excess mortality in patients achieving event-free survival for 12 or 24 months.(10) However, Sarkozy et al., reported contrary findings suggesting that subsequent cumulative incidences of lymphoma-related and non-lymphoma-related mortality were similar among patients who were event-free at 24 months.(14)

Given the prolonged PFS and OS in FL, several attempts have been made to identify earlier surrogate endpoints that might reliably predict overall survival. Event-free survival at 24 months, as well as CR at 30 months, are both associated with good prognosis.(5,15) Although we found excess mortality due to FL among non-POD24-patients, there was a substantial difference in survival between POD24- and non-POD24-patients, and the difference remained even after second-line treatment. It is likely that a longer follow-up and inclusion of a larger fraction of relapsed non-POD24-patients would improve the survival of these patients. Considering this, we suggest that studies concerning relapsed FL should be divided into two categories, based on the disease status of the patients at 24 months. This would reduce bias originating from overrepresentation of patients with early relapse in studies with a short follow-up. Non-POD24-patients have a favourable prognosis; therefore, the priority in their treatment should be to minimize lifetime treatment burden and chemotherapy-associated toxicities, as excess mortality consists not only of deaths from progressive lymphoma but also of deaths related to treatment toxicity. In contrast, POD24-patients are at risk of early death due to progressive lymphoma, which justifies more aggressive therapies coupled with higher treatment related mortality and morbidity and increased societal cost.

## AUTHOR CONTRIBUTIONS

A.R., K.S., and O.K. designed the research. R.P., M.K., E.J., S.M., M.S., and J-M.S., collected the data. A.R., M.H., R.S., O.K., and K.S. analyzed the results. A.R., K.S., and O.K. wrote the original draft. M.H. and A.R. made the figures. M.H., R.S., R.P., M.K., H.K., E.J., S.M., M.S., and J-M.S, reviewed and edited the manuscript. O.K. and K.S. supervised the study. All the authors accepted the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

The datasets generated during the current study are available from the corresponding author for reasonable requests.

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*Conflict of interest:* The authors have no relevant financial or non-financial interests to disclose.

*Ethical approval and patient consent:* The principles of the Declaration of Helsinki were followed throughout the study. The study was approved by the Regional Ethics Committee for the Northern Ostrobothnia Hospital District. Permission to use patient-related data was applied from the hospital authorities responsible for that data. No consent from patients was required for the study, as Finnish and EU legislation allows the use of register-based data for retrospective studies without the informed consent of the patients concerned.

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complete response as a surrogate end point in first-line follicular lymphoma therapy: An individual patient-level analysis of multiple randomized trials. J Clin Oncol. 2017;35(5):552–60.

**FIGURE LEGENDS:**

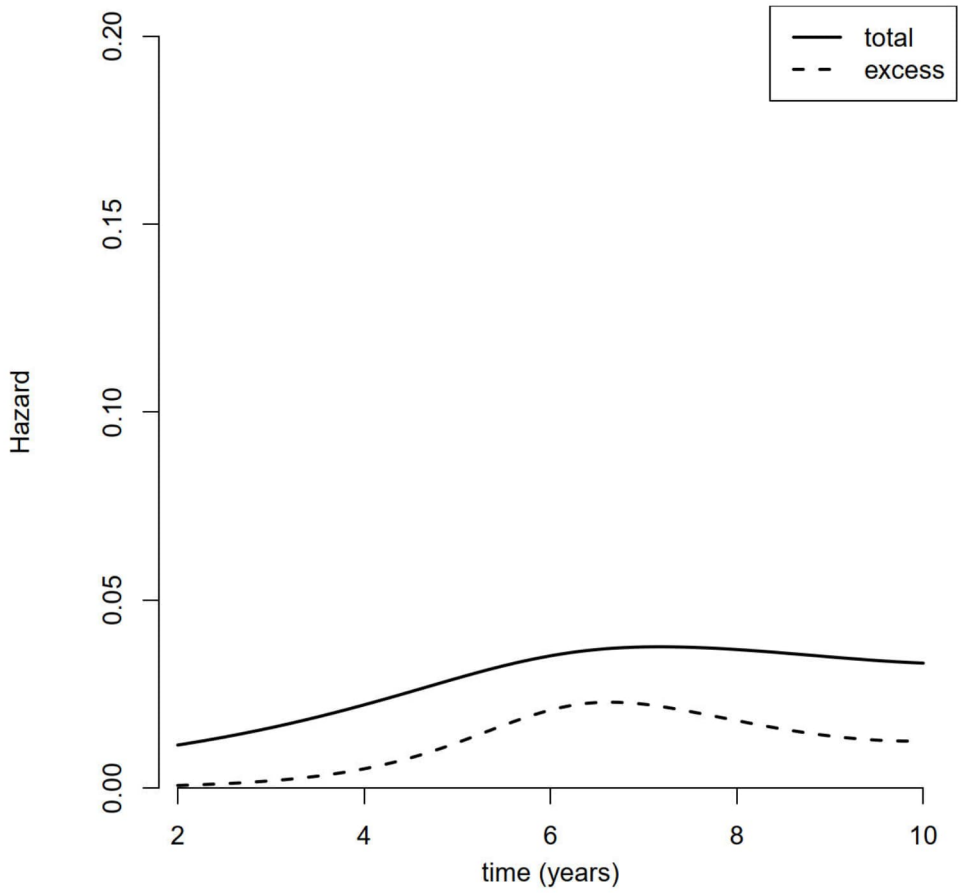
**Figure 1:** Mortality and survival of FL patients with event-free survival ≥ 24 months after first-line therapy (non-POD24-patients), relative to the control populations. Time starts from 2 years after first-line therapy. A) The total and excess mortality rates of non-POD24-patients. B) The overall and net survival rates of non-POD24-patients.

**Figure 2:** Cumulative incidence of the competing risks of cause of death. In Figure 2A and 2C, time starts from diagnosis, and in Figure 2B, time starts from 2 years after first-line therapy. A) Cumulative incidence by cause of death across the whole study population. B) Cumulative incidence by cause of death for patients who were event-free at 24 months following first-line therapy. C) Cumulative incidence by cause of death for patients with disease progression within 24 months of first-line therapy (POD24).

**Supporting Figure S1:** Flow chart explaining eligibility and inclusion for our study population.

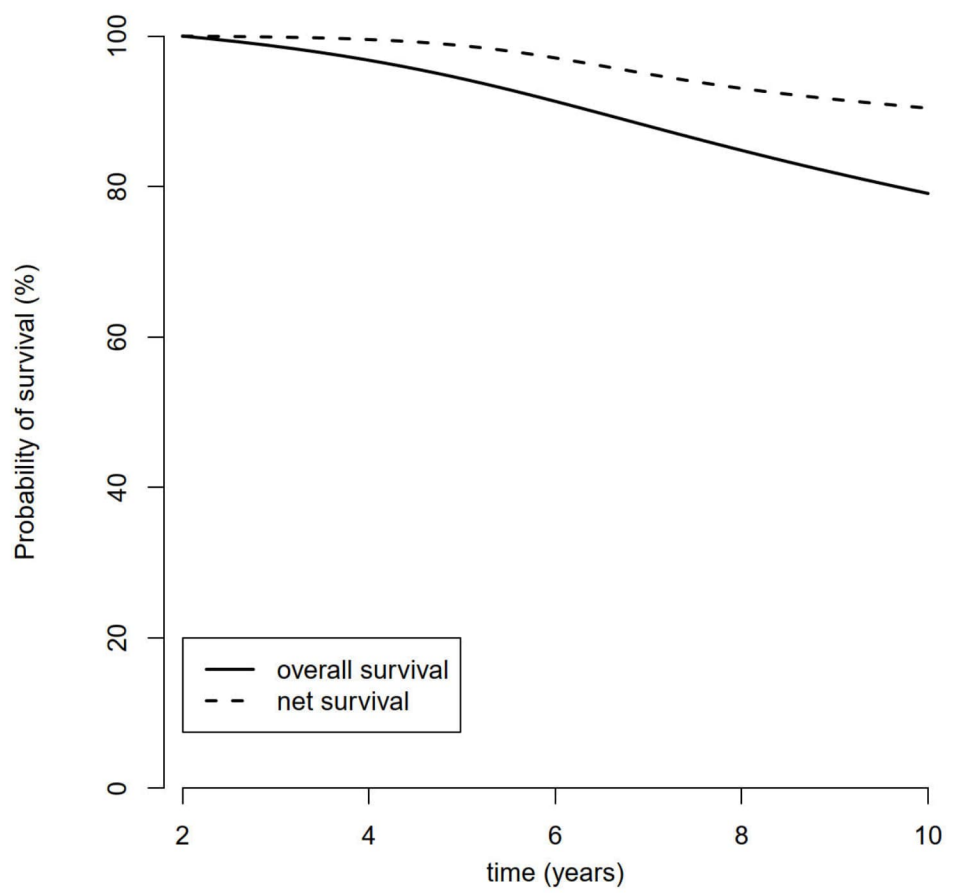
**Supporting Figure S2**: Disease-specific survival following second-line treatment in patients categorised as early event progression (POD24) and event-free survival for 24 months after first-line therapy (non-POD24).

A)

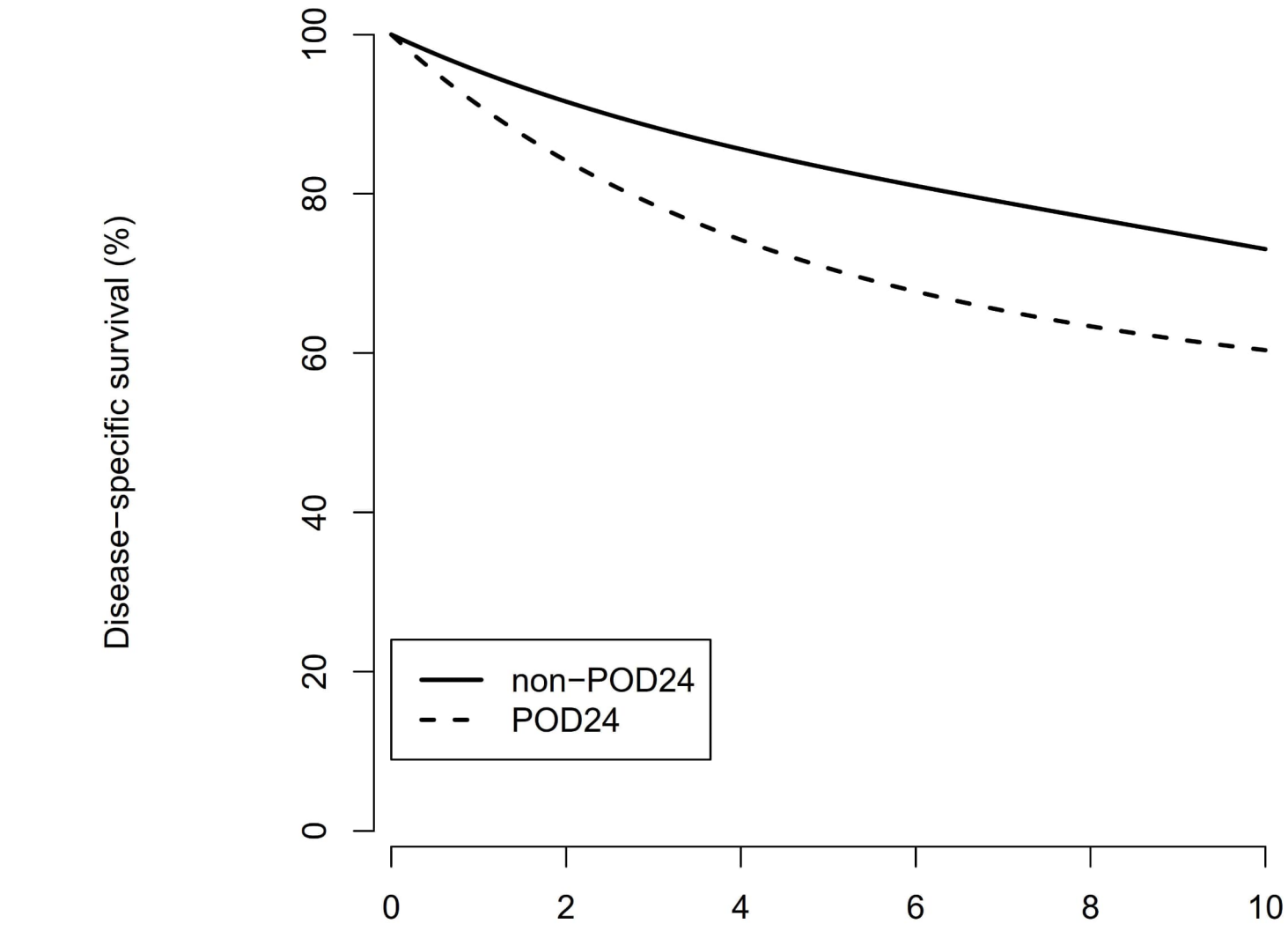



No. at risk: 627 510 370 236 134

B)




No. at risk: 627 510 370 236 134

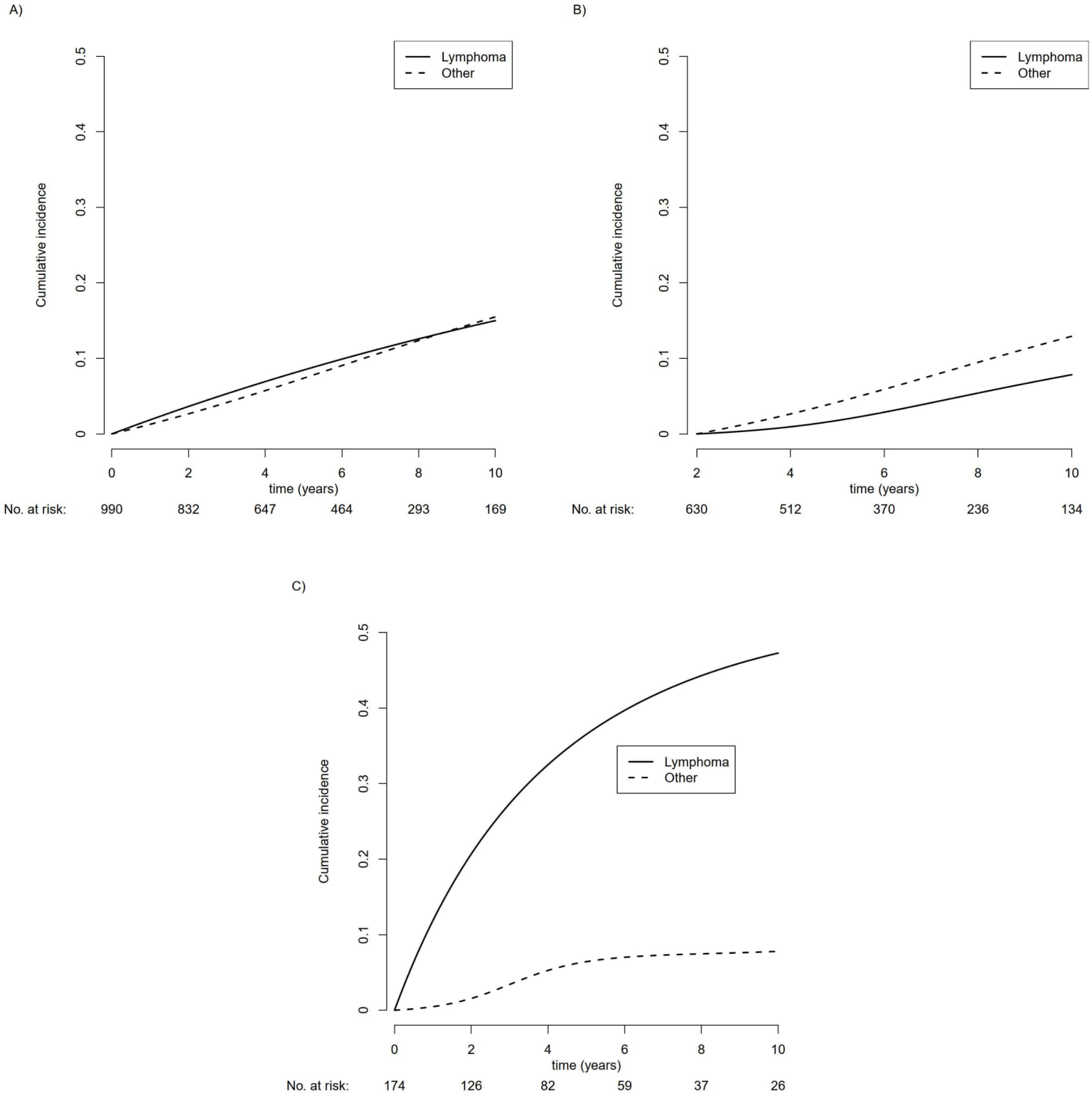


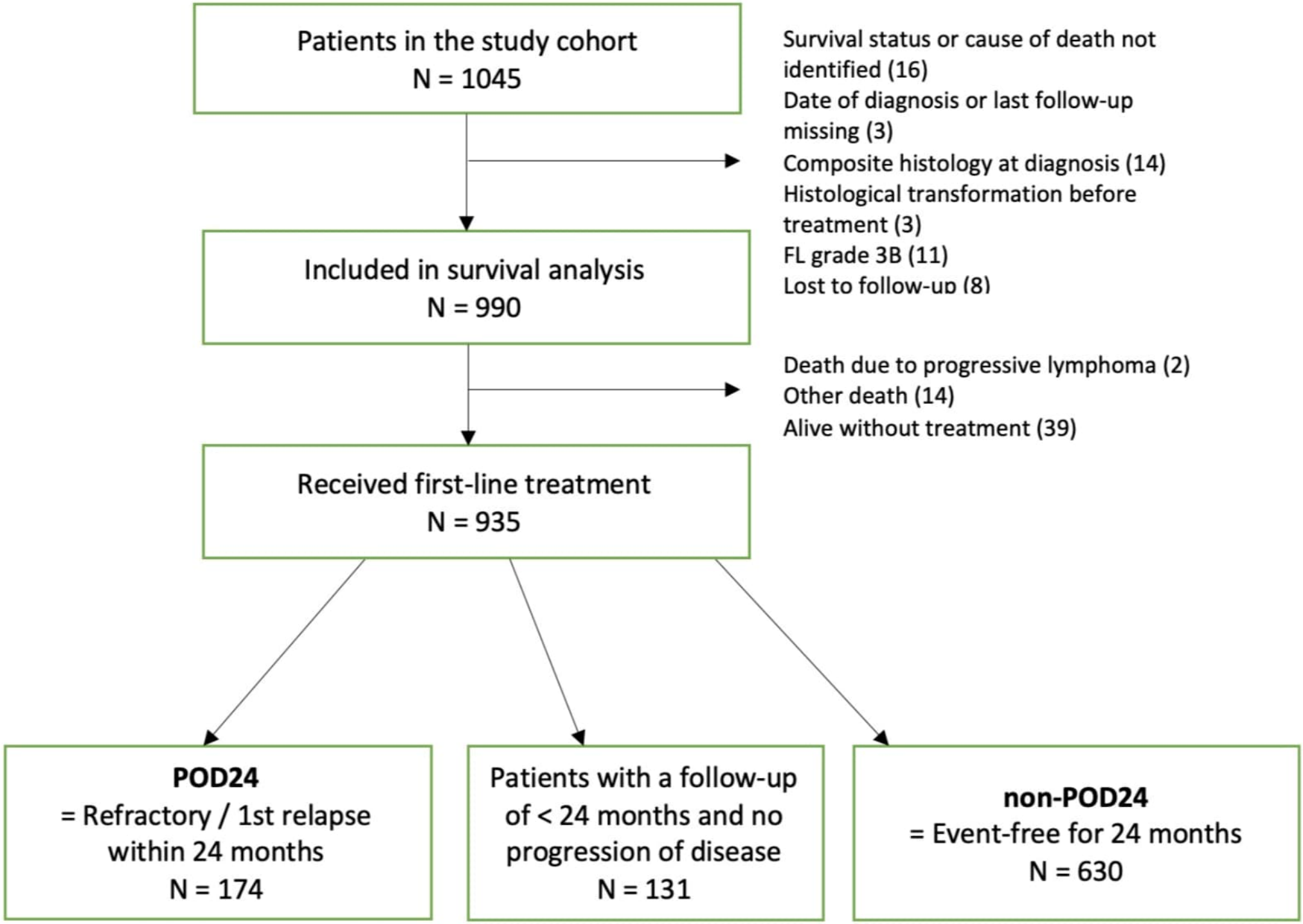

| | | | | | | |
|---|---|---|---|---|---|---|
| No. at risk non−POD24: | 145 | 107 | 71 | 48 | 28 | 14 |
| No. at risk POD24: | 94 | 66 | 41 | 26 | 17 | 12 |

| Table 1 | POD24-patients | non-POD24-patients | p-value* |
|---|---|---|---|
| **Variable** | N = 174 | N = 630 | |
| **Follow-up duration, months** | | | <0.001 |
| Median (range) | 45 (0–212) | 79 (24–224) | |
| **Age at diagnosis, years** | | | 0.002 |
| Median (range) | 61 (30–87) | 58 (17–100) | |
| **Sex** | | | 0.093 |
| Female | 81 (46.6) | 338 (53.7) | |
| Male | 93 (53.4) | 291 (46.3) | |
| NA | 0 | 1 | |
| **Grade** | | | 0.346 |
| 1 or 2 | 117 (81.3) | 490 (84.5) | |
| 3 | 27 (18.8) | 90 (15.5) | |
| NA | 30 | 50 | |
| **Stage** | | | <0.001 |
| I-II | 34 (21.0) | 212 (35.3) | |
| III-IV | 128 (79.0) | 389 (64.7) | |
| NA | 12 | 29 | |
| **FLIPI**[b] | | | <0.001 |
| 0-1 | 35 (23.3) | 223 (39.3) | |
| 2 | 34 (22.7) | 169 (29.8) | |
| 3-5 | 81 (54.0) | 175 (30.9) | |
| NA | 24 | 63 | |
| **LDH**[c] **level** | | | <0.001 |
| Normal | 69 (56.1) | 351 (72.8) | |
| Elevated | 54 (43.9) | 131 (27.2) | |
| NA | 51 | 148 | |
| **Hb** (g/dL) | | | 0.001 |
| < 12 | 36 (23.8) | 77 (13.1) | |
| ≥ 12 | 115 (76.2) | 511 (86.9) | |
| NA | 23 | 42 | |
| **B-symptoms**[d] | | | <0.001 |
| Yes | 45 (26.8) | 95 (15.4) | |
| No | 123 (73.2) | 522 (84.6) | |
| NA | 6 | 13 | |
| **Initial treatment** | | | |
| Immunochemotherapy | 118 (67.8) | 482 (76.5) | 0.020 |
| Chemotherapy without rituximab | 29 (16.7) | 59 (9.4) | 0.006 |
| Rituximab monotherapy | 2 (1.1) | 19 (3.0) | 0.172 |
| Radiation therapy only | 24 (13.8) | 64 (10.2) | 0.174 |
| Surgery only | 1 (0.6) | 4 (0.6) | 0.929 |
| NA | 0 | 2 | |
| **Maintenance with rituximab after first line therapy** | 27 (15.5) | 193 (30.6) | <0.001 |
| **Number of deaths during the follow-up** | 83 (47.7) | 92 (14.6) | |
| Cause of death | | | |
| Progressive lymphoma | 70 (84.3) | 34 (37.0) | |
| Other causes | 13 (15.7) | 58 (63.0) | |

**Table 1:** Patient characteristics stratified based on the duration of first remission. POD24 was defined as clear progression of disease within 24 months of the first-line therapy. Non-POD24 was defined as the absence of relapse, progression, or death due to any cause within 24 months of first-line therapy.

a: NA = Not available
b: FLIPI = Follicular Lymphoma International Prognostic Index
c: LDH = lactate dehydrogenase
d: B-symptoms = systemic symptoms (unexplained weight loss, fever, night sweats)
*Pearson's chi-squared test


A)
Lymphoma
Other
Cumulative incidence
0
0.1
0.2
0.3
0.4
0.5
0
2
4
6
8
10
time (years)
No. at risk:
990
832
647
464
293
169
B)
Lymphoma
Other
Cumulative incidence
0
0.1
0.2
0.3
0.4
0.5
2
4
6
8
10
time (years)
No. at risk:
630
512
370
236
134
C)
Lymphoma
Other
Cumulative incidence
0
0.1
0.2
0.3
0.4
0.5
0
2
4
6
8
10
time (years)
No. at risk:
174
126
82
59
37
26


Patients in the study cohort
N = 1045
Survival status or cause of death not identified (16)
Date of diagnosis or last follow-up missing (3)
Composite histology at diagnosis (14)
Histological transformation before treatment (3)
FL grade 3B (11)
Lost to follow-up (8)
Included in survival analysis
N = 990
Death due to progressive lymphoma (2)
Other death (14)
Alive without treatment (39)
Received first-line treatment
N = 935
POD24
= Refractory / 1st relapse within 24 months
N = 174
Patients with a follow-up of < 24 months and no progression of disease
N = 131
non-POD24
= Event-free for 24 months
N = 630