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RESEARCH ARTICLE

Treatment sequencing and impact of number of treatment lines on survival in follicular lymphoma: A national population-based study

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Abstract

Follicular lymphoma (FL) is a clinically heterogeneous disease. The need for treatment, treatment sequencing, number of treatment lines, and its association with survival have not been described in a population-based setting. We identified all patients diagnosed with FL in the Swedish Lymphoma register from 2007 to 2014, followed until 2020, with detailed data on progression/relapse, transformation, and 2nd and further lines of therapy. During a median follow-up of 6.8 years, 1226 patients (69%) received 1st systemic treatment, 358 patients (20%) were managed with watch-and-wait (WaW) only, and 188 (10%) patients were treated with radiotherapy and did not require additional therapy during the study period. Among patients starting systemic treatment, 496 (40%), 224 (18%), and 88 (7%) received 2nd-, 3rd-, or 4th-line therapy, respectively. The 10-year cause-specific cumulative incidence of transformation was 13%. Among patients managed with 1st line R-single, R-CHOP, or BR, 54%, 33%, and 29% required 2nd line, respectively. The cumulative probability of starting subsequent treatment within 2 years was 26% after 1st line and 35% after 2nd line treatment. Two-year OS following 1st, 2nd, 3rd, and 4th line systemic treatment was 84%, 70%, 52%, and 36%, respectively, and remained similar when excluding transformations. We conclude that a substantial proportion of FL patients can be managed with WaW for a long period of time, while patients who require multiple treatment lines constitute a group with a large clinical unmet need. These results constitute valuable real-world reference data for FL.

KEYWORDS
follicular lymphoma, POD24, population-based, treatment sequencing

1 | INTRODUCTION

Follicular lymphoma (FL) accounts for approximately 20% of all lymphomas. It is an indolent but most often incurable disease, with the exception of stage I-II disease that can be cured by radiotherapy (RT) [1]. FL is characterised by a vast clinical and molecular heterogeneity. Some patients have an asymptomatic, indolent disease course that is possible to manage with a watch-and-wait (WaW) approach whereas others have high tumour burden and symptomatic disease that requires immediate systemic treatment [2, 3]. Further, response to, and duration of remission of, 1st line treatment varies [2, 4]. Concordantly, reported 10-year overall survival (OS) ranges between 54% in a population-based setting [4] and 80% in a study of FL patients managed at referral centres in France and USA [5]. Encouraging survival in recent decades reflects a more effective therapy both at 1st and subsequent treatment lines [6]. However, approximately 20% of patients with FL are reported to progress within 24 months of 1st line systemic treatment (POD24), which has been associated with inferior survival in several studies [5, 7-13]. Also, the duration of response has been shown to decrease with an increased number of treatment lines in a few studies [14, 15]. Patients with recurring relapses may thus also constitute a group with a clinical unmet need, but are as yet more sparsely described.

The choice of treatment in FL is based on both patient- and disease-related factors [16]. Treatment sequencing and how number of treatment lines impacts OS and time to next treatment has not yet been specifically studied in a comprehensive population-based setting. Therefore, we aimed to describe the treatment patterns, including 1st and subsequent systemic treatment lines, time to next treatment and OS in a consecutive real-world cohort of all patients diagnosed with FL in Sweden from 2007 to 2014, followed through 2020.

2 | MATERIALS AND METHODS

2.1 | Sources of data

All patients diagnosed with FL between 2007 and 2014 in the Swedish Lymphoma Register (SLR) were included with the exclusion of patients with primary cutaneous FL. The SLR was initiated in 2000 and has a coverage of >95% compared with the nationwide Swedish Cancer Register to which all incident cancer diagnoses are reported by law [17]. The SLR records detailed data on patient- and clinical characteristics at diagnosis, first-line treatment, and progression. For this study, the register data was validated and supplemented with data on progression/relapse, transformation, and 2nd and further lines of therapy from a medical chart review, with follow-up through 2020, as previously described [12]. In Sweden, all residents diagnosed with FL are managed in specialist care in oncology or haematology through the public tax-funded health care system. Transformations were defined as morphologically verified transformations only. The main cause of death was obtained through linkage to the cause-of-death register. The study was approved by the Ethical Review Board in Stockholm, Sweden (2015-202831).

2.2 | Study population

A total of 2079 registered patients were identified as eligible for the study. Medical chart review could be completed for 2046 FL patients (98%). Non-completion was primarily due to a lack of active consent and inaccessible medical records. Patients who were diagnosed with FL grade 3B ($n = 68$) or transformed FL ($n = 156$) were excluded after review as were patients with treatment but no information on the date or type of treatment ($n = 50$). The final study population comprised 1772 patients (Figure 1).

2.3 | Treatment definition

We focused on investigating the number and sequencing of lines of systemic therapies during follow-up. Patients who were managed with RT only as 1st line treatment or a WaW approach at diagnosis were thus included in survival analyses only if they eventually required systemic treatment. Initial WaW was defined as no treatment within the first 6 months from diagnosis. Consolidation treatment including RT, allogeneic or autologous stem cell transplantation (ASCT), or maintenance with anti-CD20 antibody therapy was noted but did not count as separate treatment lines. Treatment groups of main interest were R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), BR (bendamustine, rituximab), and R-single. Other treatments included R-FC (fludarabine, cyclophosphamide), R-CVP (cyclophosphamide, vincristine, prednisone), chlorambucil and other at the time more uncommonly used drugs and combinations (e.g., lenalidomide, idelalisib, trophosphamide, cyclophosphamide, R-Zevalin, gemcitabine, cytarabine, methotrexate). Salvage therapies were defined as platinum-based treatments or IME (ifosfamide, methotrexate, etoposide).

2.4 | Statistics

Frequencies and proportions of demographic, clinical, and follow-up characteristics were calculated by the type of first-line systemic treatment (R-single, BR, R-CHOP and all others). The frequency and proportion of different systemic therapies, and the changes across treatment lines 1–4, were visualized using a Sankey diagram (using the R package ggsankey), overall and stratified by POD24. Additionally, a Sankey diagram was used to illustrate the outcome after 1st line treatment (no additional treatment, death within 2 years, death ≥2 years, 2nd-line treatment within 2 years, or 2nd-line treatment ≥2 years). Follow-up started on the date of current treatment initiation and ended on the date of next line initiation, date of death, or end of the study period, whichever came first. The end of the study period varied between December 31, 2018, and December 31, 2020, depending on

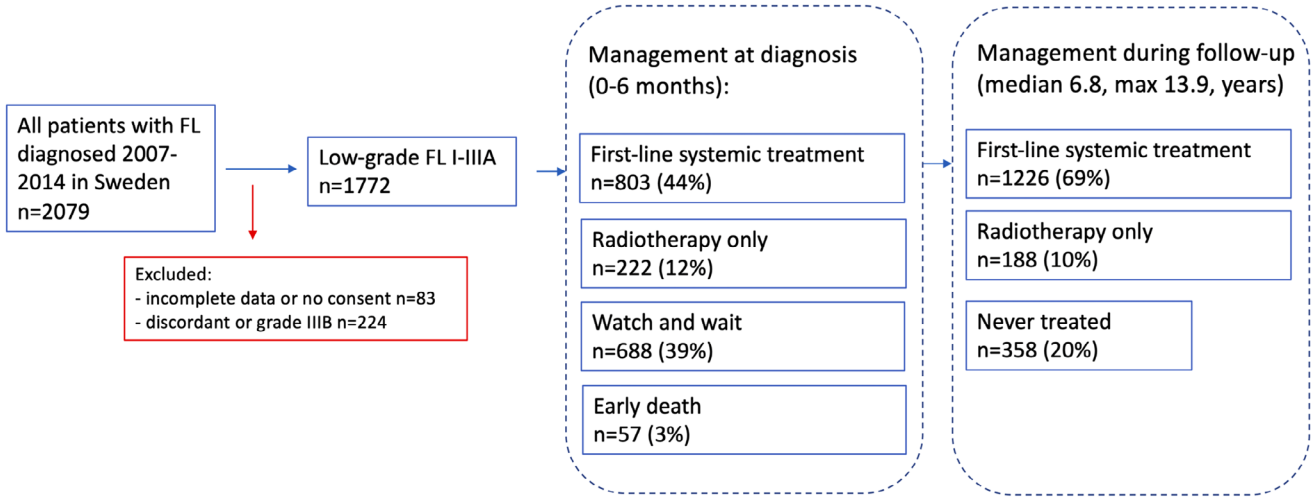


FIGURE 1 Flowchart of included patients.

when data collection was performed. The cumulative probability of transformation was estimated in the presence of the competing risk of death. Non-parametric cumulative probabilities of subsequent treatment were estimated in the presence of the competing risk of death using the Stata package stcompet. Two-year point estimates with 95% confidence intervals (CIs) and time points (in years) when 20% of patients had required a subsequent treatment were extracted and tabulated for all and with transformation as treatment indication for the previous line excluded. Additionally, the cumulative probability of a 2nd line treatment was estimated by R-CHOP, BR, and R-single in 1st line.

Lastly, OS overall and after 1st, 2nd, 3rd, and 4th line treatment (follow-up started as described above) was calculated using the Kaplan-Meier method, for (A) all patients, (B) patients who did not have transformation as treatment indication, and (C) patients who received either R-CHOP, BR, or R-single in 1st line treatment.

The main analyses were done in Stata (StataCorp. Stata Statistical Software: Release 18: StataCorp LLC.) and the Sankey diagrams in R (version 4.1.3).

3 | RESULTS

3.1 | Patient characteristics and 1st line treatment

A total of 1772 patients with FL were included in the final study cohort (Table 1, Figure 1). Median age at diagnosis was 67 (18–98) years and median follow-up time was 6.8 (interquartile range (IQR) 4.7–9.1) years. In total, 688 (39%) of patients were managed with initial WaW. During follow-up, 330 (48%) went on to require systemic treatment while 358 (52% or 20% of the entire study population) were managed with only WaW until censoring. Of these, 132/358 died during follow-up of whom 47 (36%) had lymphoma registered as cause of death (data not shown). Patients managed with WaW during the whole follow-up period had a median age of 70 years at diagnosis and the proportion of patients with a low-risk follicular lymphoma international prognostic index (FLIPI) score was 50%, compared with 28% among patients who received systemic treatment (data not shown). Overall, 222 (12%) patients received RT with curative intent at diagnosis of which 188 (85%) did not require subsequent treatment during follow-up. Thirty-one patients died of whom 8 (26%) patients had lymphoma registered as cause of death.

At diagnosis or during follow-up, 1226 (69%) patients received systemic 1st line therapy. Type and patient characteristics by 1st line treatment are presented in Table 1. Diagnosis to treatment intervals for R-CHOP, BR, and R-single were 38 days (IQR: 18–288 days), 52.5 days (IQR 28–321 days) and 105 days (IQR: 48–530), respectively. The temporal trend in the use of R-single, R-CHOP, BR, and other therapies as 1st line treatment over the study period is illustrated in Figure 2.

3.2 | Number of treatment lines, type of treatment, and transformation

Systemic therapy types across treatment lines are presented in Figure 3. A total of 496 patients (40% of patients with systemic 1st line treatment) received a systemic 2nd line treatment. Here, BR was most commonly used (153, 31%) followed by R-CHOP (141, 28%) and R-single (67, 14%). Subsequently, 224 (18%) patients received 3rd line treatment, and 88 (7%) patients received 4th line. The maximum number of treatment lines was 7 (≥5 lines: $n = 41$, 3.3%).

The cumulative probability of transformation in the presence of the competing risk of death was 13% at 10 years (Figure S1). The number of patients who had a first or relapsed transformation as treatment indication and the use of consolidative RT, consolidative ASCT and R maintenance, are presented in Figure 3.

A Sankey plot stratified by the three most common 1st line treatments, and all other treatments grouped together, with their subsequent outcomes is presented in Figure 4. Overall, 33%, 29%, and 53% of patients treated with R-CHOP, BR, and R-single in 1st line received

TABLE 1 Characteristics of patients diagnosed with follicular lymphoma (FL) 2007–2014 and followed through 2020 in Sweden, overall, by any first-line systemic treatment, and by first-line systemic treatment type.

			1st-line systemic treatment type			
	All patients	Any 1st-line systemic treatment	R-CHOP	BR	R-single	Other[a]
Total, *n* (row %)	1,772	1,226	449 (36.6)	194 (15.8)	374 (30.5)	209 (17.1)
Diagnosis age, median (range)	67 (18-98)	66 (24-98)	66 (24-96)	66 (31-90)	64 (27-91)	73 (36-98)
Sex, *n* (col %)						
Male	837 (49.0)	610 (49.8)	235 (52.3)	98 (50.5)	163 (43.6)	114 (54.6)
Female	903 (51.0)	616 (50.2)	214 (47.7)	96 (49.5)	211 (56.4)	95 (45.5)
Diagnosis year, n (col %)						
2007–2010	837 (47.2)	608 (49.6)	252 (56.1)	34 (17.5)	178 (47.6)	144 (68.9)
2011–2014	935 (52.8)	618 (50.4)	197 (43.9)	160 (82.5)	196 (52.4)	65 (31.0)
Stage, *n* (col %)						
Ann Arbor I	365 (20.6)	136 (11.1)	39 (8.7)	17 (8.8)	57 (15.2)	23 (11.0)
Ann Arbor II	320 (18.1)	227 (18.5)	79 (17.6)	39 (20.1)	70 (18.7)	39 (18.7)
Ann Arbor III	483 (27.3)	377 (30.8)	140 (31.2)	56 (28.9)	124 (33.2)	57 (27.3)
Ann Arbor IV	565 (31.9)	479 (39.1)	187 (41.7)	82 (42.3)	123 (32.9)	87 (41.6)
Missing	39 (2.2)	7 (0.6)	4 (0.9)	0 (0.0)	0 (0.0)	3 (1.4)
FLIPI, *n* (col %)						
Low risk	630 (35.6)	339 (27.7)	96 (21.4)	54 (27.8)	133 (35.6)	56 (26.8)
Middle risk	471 (26.6)	357 (29.1)	118 (26.3)	54 (27.8)	126 (33.7)	59 (28.2)
High risk	567 (32.0)	512 (41.8)	231 (51.5)	81 (41.8)	111 (29.7)	89 (42.6)
Missing	108 (5.9)	18 (1.5)	4 (0.9)	5 (2.6)	4 (1.1)	5 (2.4)
WHO performance status, *n* (col %)						
<2	1,639 (92.5)	1,136 (92.7)	411 (91.5)	179 (92.3)	365 (97.6)	181 (86.6)
2+	91 (5.1)	68 (5.6)	26 (5.8)	13 (6.7)	6 (1.6)	23 (11.0)
Unclear	42 (2.4)	22 (1.8)	12 (2.7)	2 (1.0)	3 (0.8)	5 (2.4)
Grade, *n* (col %)						
1	464 (26.2)	293 (23.9)	93 (20.7)	38 (19.6)	96 (25.7)	66 (31.6)
2	712 (40.2)	513 (41.8)	170 (37.9)	94 (48.5)	165 (44.1)	84 (40.2)
3A	343 (19.4)	246 (20.1)	117 (26.1)	31 (16.0)	71 (19.0)	27 (12.9)
Low-grade UNS/unclear	253 (14.3)	174 (14.2)	69 (15.4)	31 (16.0)	42 (11.2)	32 (15.3)
RT before first systemic treatment, *n* (col %)						
No	NA	1,146 (93.5)	428 (95.3)	181 (93.3)	340 (90.9)	197 (94.3)
Yes	NA	80 (6.5)	21 (4.7)	13 (6.7)	34 (9.1)	12 (5.7)
Transformation as treatment indication, *n* (col %)						
No	NA	1,138 (92.8)	367 (81.7)	192 (99.0)	371 (99.2)	208 (99.5)
Yes	NA	88 (7.2)	82 (18.3)	2 (1.0)	3 (0.8)	1 (0.5)
Start of systemic treatment ≥6 months from diagnosis (initial WaW), *n* (col %)						
No	NA	896 (73.1)	343 (76.4)	147 (75.8)	240 (64.2)	166 (79.4)
Yes	NA	330 (26.9)	106 (23.6)	47 (24.2)	134 (35.8)	43 (20.6)

Note: Due to rounding, not all percentages add up to 100%.

Abbreviations: Bendamustine Rituximab, R; column, FLIPI; Follicular lymphoma international prognostic index, RT; n;not applicable.; number, col; Radiotherapy, WaW; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, BR; Rituximab, NA; Watch&Wait, R-CHOP.

[a]Other treatments included R-FC (fludarabine, cyclophosphamide), R-CVP (cyclophosphamide, vincristine, prednisone), chlorambucil and other more uncommonly used drugs and combinations (e.g., lenalidomide, idelalisib, trophosphamide, cyclophosphamide, R-Zevalin, gemcitabine, cytarabine, methotrexate).

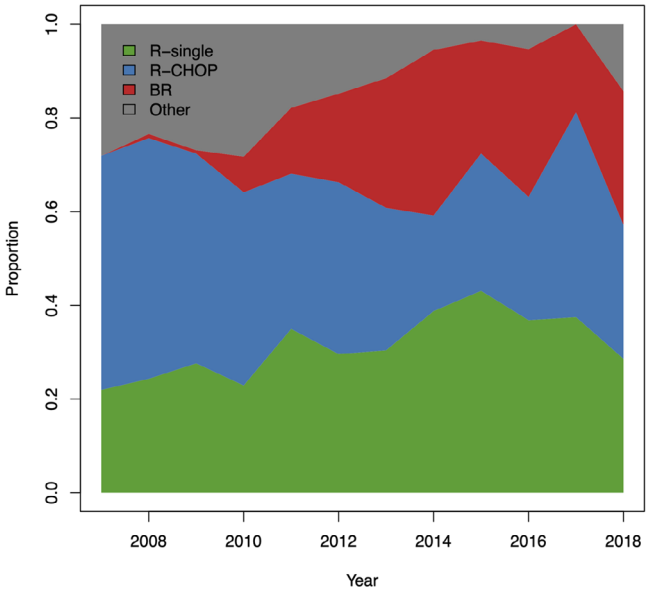


FIGURE 2 Temporal trends in administration of R-CHOP, BR, and R-single as first-line systemic treatment by date of treatment initiation among patients diagnosed with follicular lymphoma (FL) 2007–2014 and followed through 2020[a] in Sweden. BR, Bendamustine rituximab; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone. [a]Proportions are shown up to 2018 due to small numbers of patients in the cohort initiating 1st line in 2019 and 2020.

2nd line treatment at any time point during follow-up. The corresponding proportion of POD24 were 21%, 18%, and 33% for R-CHOP, BR, and R-single (Figure 4). Further, 51%, 57%, and 37% of patients treated with R-CHOP, BR, and R-single, respectively, were alive at the end of follow-up without the need for 2nd line treatment (Figure 4).

3.3 | Time to next treatment

The cumulative probability, in the presence of the competing risk of death, of needing a 2nd line treatment was 26% at 2 years, with a plateau at four years (Figure 5A). Following 2nd line treatment, the cumulative probability of receiving a 3rd line within two years was 35% and remained similar after 3rd and 4th line (Figure 5A). The cumulative probability of starting a 2nd line treatment at two years was 34% after R-single in 1st line, 21% after R-CHOP, and 19% after BR (Figure 5B) with similar proportions with transformations excluded (Figure S2).

3.4 | Treatment sequencing by POD24

Of all 496 patients who received 2nd line treatment, 316 (64%) did so within 2 years, that is, 17.8% POD24 in the whole population and 25.7% in the cohort with systemic 1st line treatment (Figure 4). Among patients with a 2nd line treatment within two years, 32% received R-CHOP as 2nd line, compared with 24% among patients with treatment indication ≥2 years from 1st line treatment 24% (Figure S3A, B). Among 98 patients who had transformation as an indication for 2nd line treatment, 66 (67%) presented with POD24.

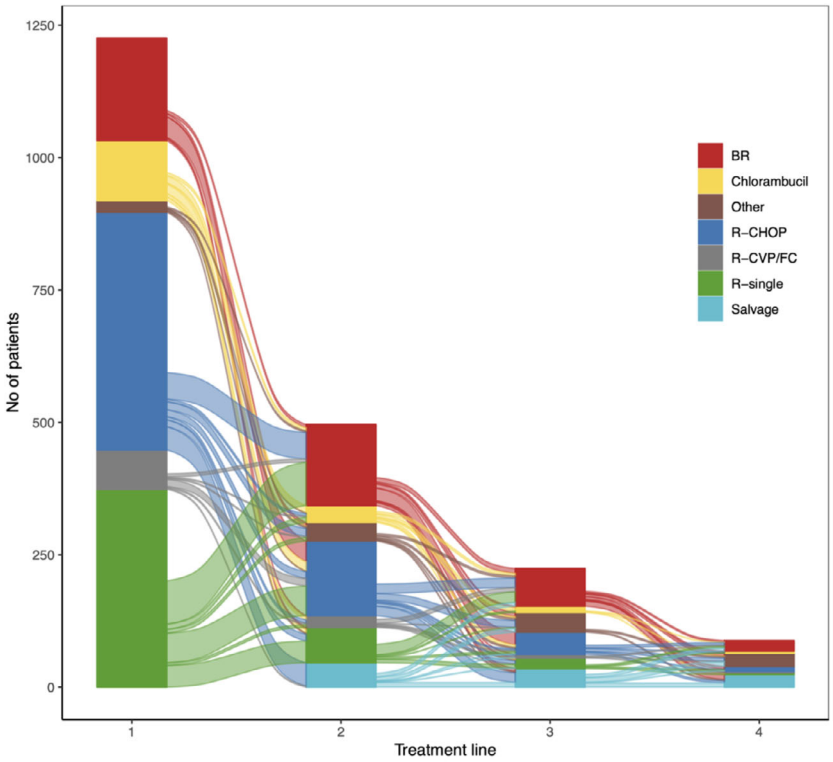
3.5 | Survival

The 5-year OS from diagnosis for the whole patient population was 77% (95% CI:75-79%). From 1st line systemic therapy 5- & 2-year OS were 72% (95% CI: 69–75%) and 84% (95% CI: 82–86%). Of 450 (37%) patients who received 1st line treatment who died during follow-up, 276 (61%) had lymphoma registered as cause-of-death (data not shown), with a similar proportion among all 1st line treatments. The 2-year OS after 2nd, 3rd, and 4th line of therapy was 70% (95% CI: 66–74%), 52% (95% CI: 45–59%), and 36% (95% CI: 26–47%), respectively (Figure 6A). Corresponding 2-year survival proportions following initiation of 1st, 2nd, 3rd and 4th treatment lines among non-transformed patients were 85% (95% CI: 82–87%), 73% (95% CI: 68–77%), 55% (95% CI: 47–62%), and 42% (95% CI: 29–54%) (Figure 6B).

4 | DISCUSSION

We report novel comprehensive national real-world data on the need for, type, and sequencing of treatment in patients with FL and its impact on survival with up to 14 years of follow-up. Approximately 40% of patients received more than one systemic treatment line, whereas 20% were managed with WaW during the whole follow-up period. We show that the likelihood of a subsequent treatment increased, and survival decreased, by number of treatment lines. The cumulative probability of transformation was 13% and survival proportions and subsequent treatment probabilities remained largely similar when excluding transformations at each treatment line. These results provide valuable reference data for the design and interpretation of clinical studies in FL.

Previous studies reporting treatment sequencing and subsequent survival in FL have mainly included patients managed in a tertiary setting, identified from insurance records or noncomprehensive databases, or only included a limited number of treatment lines [2, 14, 18-20]. The unselected nature of our data set is reflected in the higher median age in our cohort (67 years), compared with previous studies [14, 18, 19]. Further, we report data on all treatment lines and include patients with transformation as treatment indications, providing a realistic overview of the clinical heterogeneity and treatment panorama in FL. Although it is not surprising that prognosis is poor for patients who require multiple treatment lines, survival proportions in our study are inferior compared with survival rates reported from 3rd line treatment and onwards in the LEO cohort [18] and in a study from a tertiary single centre cohort [14] but in line with previous population-based investigation.[4] Again, this likely reflects the unselected nature of our patient population. Also, in the LEO cohort, patients were indexed at 3rd line treatment and thus high-risk patients



	Treatment line					
	1	2	3	4	≥5	Total
Systemic Treatment Type	*n (col %)*	*n (col %)*	*n (col %)*	*n (col %)*	*n (col %)*	*n (%)*
R-single	374 (30.5)	67 (13.5)	20 (8.9)	3 (3.4)	1 (2.4)	
R-CHOP	449 (36.6)	141 (28.4)	42 (18.8)	9 (10.2)	4 (9.8)	
R-CVP/FC	74 (6.0)	22 (4.4)	7 (3.1)	3 (3.4)	1 (2.4)	
BR	194 (15.8)	153 (30.9)	71 (31.7)	20 (22.7)	8 (19.5)	
Chlorambucil	113 (9.2)	32 (6.5)	12 (5.4)	4 (4.6)	1 (2.4)	
Salvage*	0 (0)	46 (9.3)	35 (15.6)	24 (27.3)	4 (9.8)	
Other**	22 (1.8)	35 (7.1)	37 (16.5)	25 (28.4)	22 (53.7)	
Total	**1,226**	**496**	**224**	**88**	**41**	
Transformation as treatment Indication						
First transformation (% per line)	88 (7.2)	80 (16.1)	23 (10.2)	7 (8.0)	4 (9.8)	200 (9.6)
Relapse from transformation (% per line)	0	18 (3.6)	19 (8.4)	15 (17.1)	11 (26.8)	63 (3.0)
Total (% per line)	88 (7.2)	98 (19.7)	42 (18.6)	22 (25.1)	15 (36.6)	263 (12.6)
Consolidative/maintenance treatment						
ASCT (% per line)	9 (0.7)	37 (7.4)	22 (9.8)	8 (9.1)	0 (0.0)	76 (3.7)
Consolidative RT (% per line)	28 (2.3)	13 (2.6)	5 (2.6)	3 (3.4)	3 (7.3)	52 (2.5)
R Maintenance (% per line)	273 (22.3)	53 (10.7)	17 (7.6)	2 (2.3)	1 (2.4)	346 (16.7)

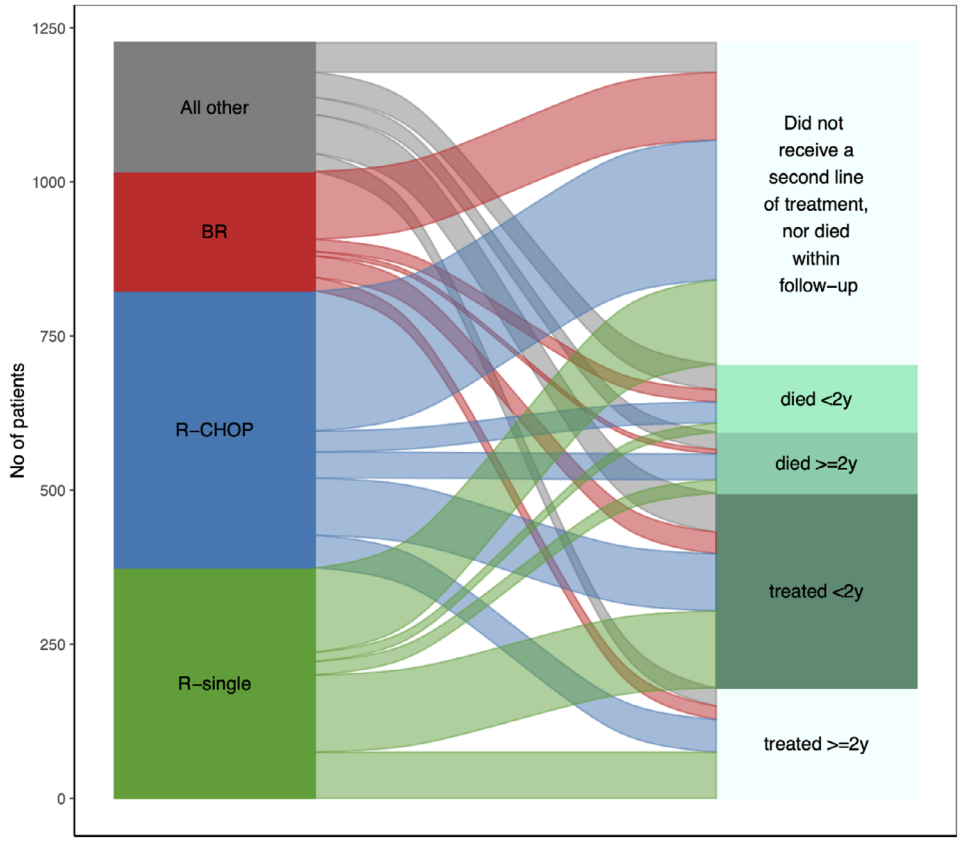
*Salvage treatments were defined as platinum-based treatment or IME (ifosfamide, methotrexate, etoposide). **Other treatments include lenalidomide, idelalisib, trophosphamide, cyclophosphamide, R-Zevalin, gemcitabine, cytarabine, methotrexate **Abbreviations:** n; number, col; column, BR; Bendamustine R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab, R; rituximab, FC; Fludarabine cyclophosphamide, CVP; cyclophosphamide, vincristine, prednisone, ASCT; Autologous stem cell transplantation, RT; Radiotherapy, Due to rounding, not all percentages add up to 100%.

FIGURE 3 Sankey diagram showing the distribution and re-distribution of systemic treatment types across treatment lines 1, 2, 3, and 4 among patients diagnosed with follicular lymphoma (FL) 2007–2014, followed through 2020 in Sweden. The exact proportion of patients by treatment type are presented in the table below, along with treatment indication (transformation) and use of maintenance/consolidative treatment, by treatment line.

with early transformation or death were not included [18]. Further, the proportion of patients with high-risk FLIPI scores was lower (23%) in both these prior studies [14, 18], compared with our population (42%).

As expected, patients with POD24 predominated among patients who required multiple treatment lines. Further, R-CHOP was more commonly used as 2nd line treatment for patients with POD24 compared with patients with later relapse, indicating a clinically more high-risk disease. Predictive markers for risk of early progression/relapse and for identifying patients who will have long-lasting remission to specific 1st line treatments in FL remain to be determined [6, 21, 22].

The clinical heterogeneity of FL is exemplified by the 20% of patients in our cohort who did not require treatment and were managed with WaW during the whole follow-up period, in contrast to the 18% of patients who instead required three or more treatment lines. The observed proportion of patients managed with a WaW approach is slightly higher than reported previously [2, 14, 23]. Further,



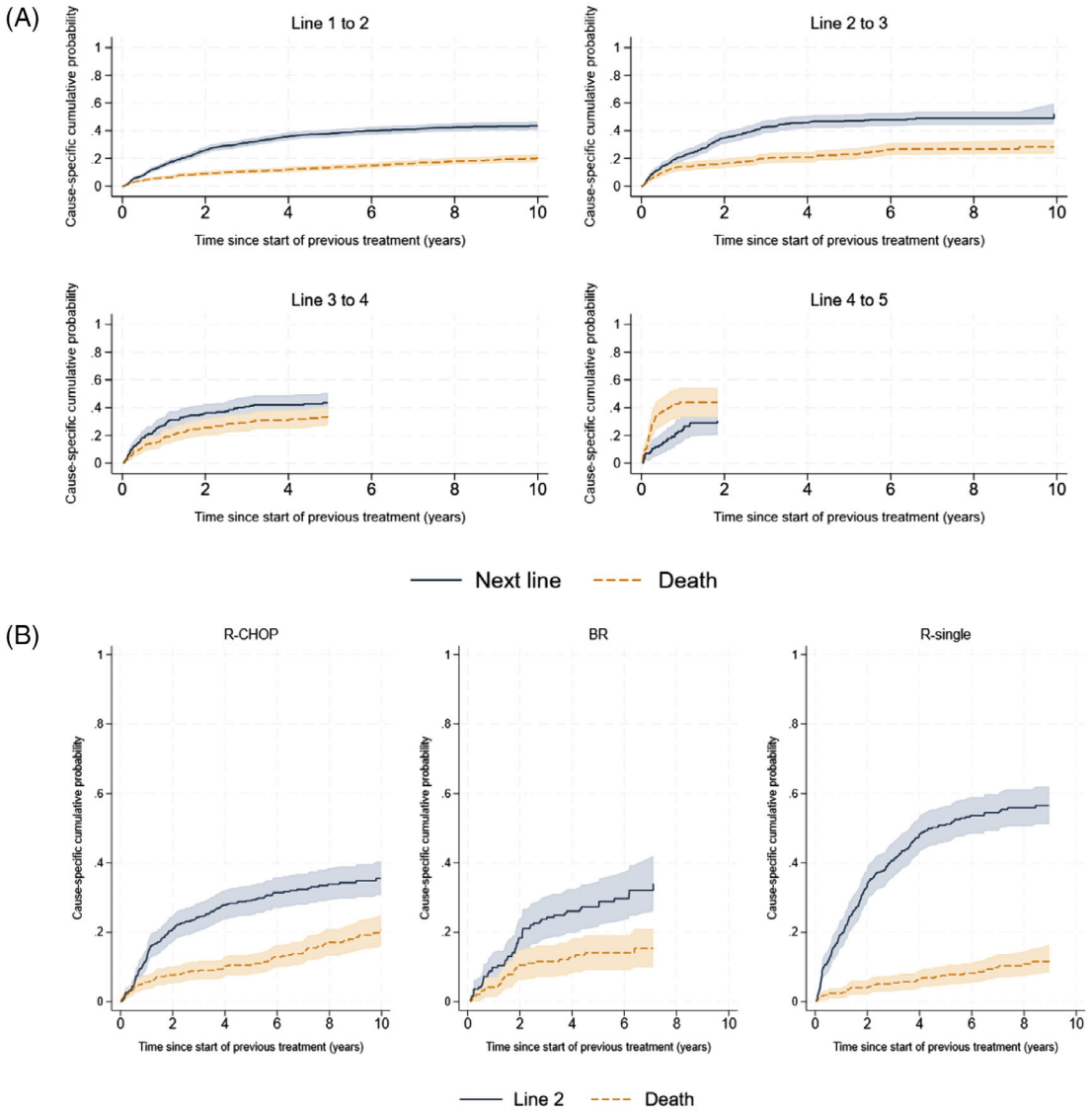
	Alive and no 2nd line n (row %)	Died within 2 years from 1st line n (row %)	Died >2 years from 1st line n (row %)	2nd line treatment within 2 years n (row %)	2nd line treatment ≥2 years n (row %)
All other	48 (23)	41 (20)	28 (13)	63 (30)	29 (14)
BR	110 (57)	20 (10)	7 (4)	35 (18)	22 (11)
R-CHOP	227 (51)	34 (8)	42 (9)	93 (21)	53 (12)
R-single	137 (37)	15 (4)	22 (6)	125 (33)	75 (20)

Abbreviations: BR; Bendamustine rituximab, R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, R; rituximab, 2y; 2 years. Median follow-up was 6.8 years, interquartile range, IQR, 4.7-9.1.

FIGURE 4 Sankey diagram showing the distribution of follicular lymphoma (FL) patients by type of 1st line systemic treatment (BR, R-CHOP, R-single, all other) and re-distribution of 2nd line and death (within or after 2 years), and being alive at end of follow-up[a] without need for additional treatment.

a smaller proportion of patients managed with initial WaW needed systemic treatment during the follow-up period (48%) than what has been described in other WaW cohorts with similar follow-up time [3, 23]. The majority of WaW patients who died during follow-up, did so due to causes other than lymphoma, whereas the majority of deceased patients with FL who required systemic treatment had lymphoma registered as cause-of-death. Similarly, of 222 patients treated with curative intent RT at diagnosis, 85% remained in remission and did not require additional treatment during follow-up, and those who died did so mostly of other causes. These results are in line with those seen in studies of PET-staged I-II FL patients who received RT [1].

In most previous studies examining treatment sequencing, most patients have received R-CHOP in 1st line or chemotherapy type is not reported [2, 14, 20]. Thus, our data on the outcomes and subsequent treatment needs of patients managed with BR in 1st line are novel. We observe that a slightly lower proportion of patients managed with BR in 1st line received 2nd line treatment, 29% compared with 53% and 33% of patients who received R-single or R-CHOP in 1st line. Concurrently, the use of BR increased during recent time periods while the use of R-CHOP decreased, in accordance with updated treatment recommendations [18, 24]. The follow-up time for patients treated with BR is thus slightly shorter than for other 1st line systemic therapies which may partly explain the lower likelihood of a 2nd line treatment, but not the lower risk of POD24 (since all patients had a potential follow-up exceeding two years). Although we observe a slightly higher proportion of patients without the need for subsequent treatment with BR (57%) we have, due to the observational nature of this study and the inherent risk of confounding by indication, refrained from comparing survival by specific treatment sequencing.

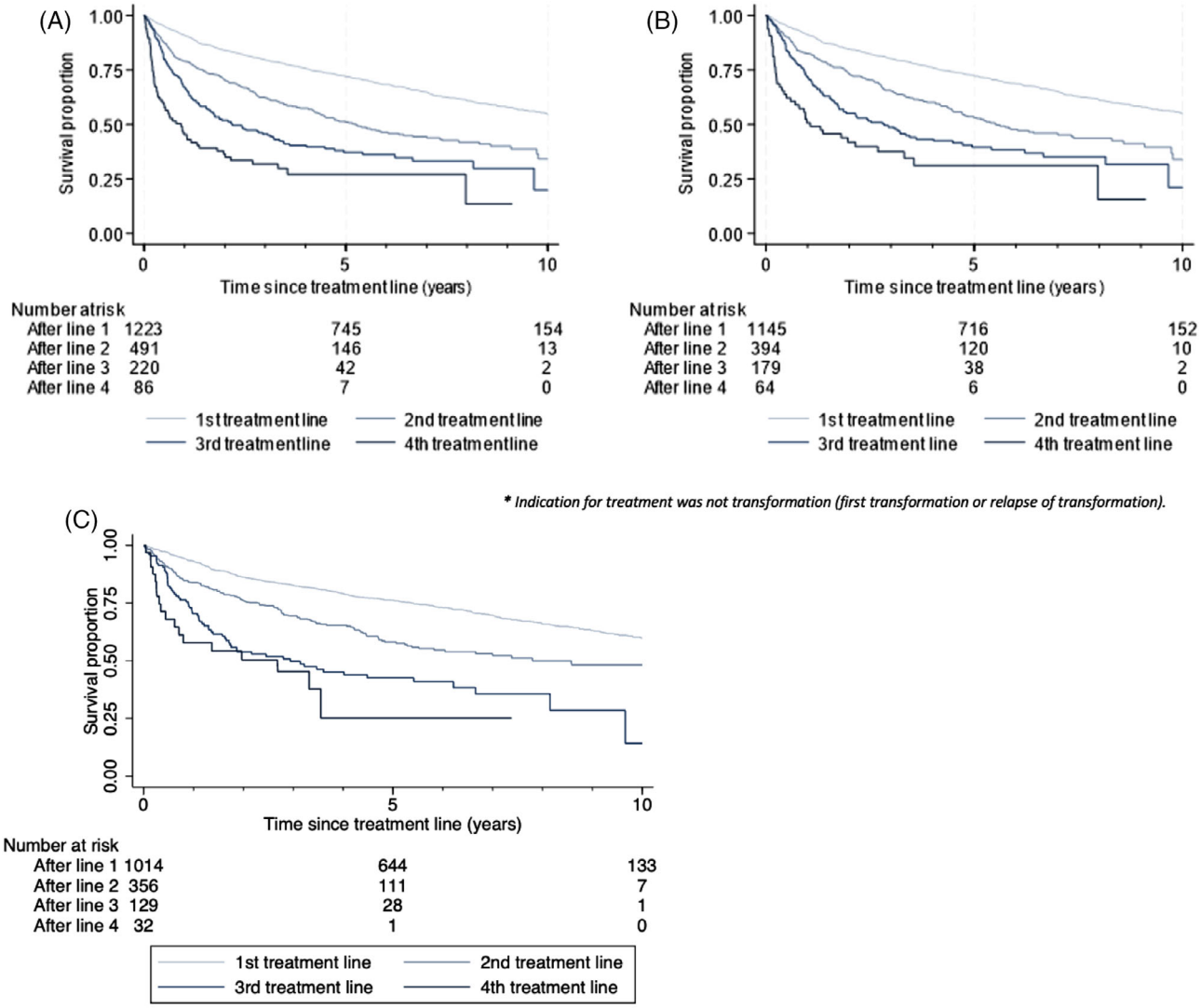


A	Line 1 to 2	Line 2 to 3	Line 3 to 4	Line 4 to 5
2-year cumulative probability (95% CI)	26% (24%-28%)	35% (31%-39%)	36% (30%-43%)	32% (22%-42%)
Time point (in years) when 20% have required subsequent treatment	1.4	0.8	0.6	0.8

B	R-CHOP	BR	R-single
2-year cumulative probability (95% CI)	21% (17%-25%)	19% (13%-24%)	34% (29%-39%)
Time point (in years) when 20% have required subsequent treatment	1.9	2.1	1.1

FIGURE 5 (A, B) Cumulative probability of starting a subsequent treatment line (solid curve) or dying (due to any cause, dashed curve), among patients diagnosed with follicular lymphoma (FL) 2007–2014 and starting any systemic treatment through 2020 in Sweden. Point estimates of the 2-year cumulative probability of a next treatment line with 95% confidence intervals (CIs) and time point of reaching 20% are shown in the table below the graphs.

In our cohort, the most commonly administered 2nd line treatment was BR, followed by R-single. Similar trends have been observed in other studies that have categorised treatment patterns in FL [2, 14, 18]. Moreover, a higher proportion of patients managed with R-single who require 2nd line treatment has been observed in previous studies that have examined the incidence of POD among patients managed with immunotherapy only [8, 10, 25]. However, as we have previously shown, this does not appear to have an unfavourable impact on overall survival [12]. The fact that the median age for patients who received R-single in 1st line was lower than for other systemic therapies in our



A: Among all patients	1st line	2nd line	3rd line	4th line
Median follow-up time	6.0 (0-13.8)	3.1 (0-12.2)	1.5 (0-10.3)	0.7 (0-9.1)
2-year OS (95% CI)	0.84 (0.82-0.86)	0.70 (0.66-0.74)	0.52 (0.45-0.59)	0.36 (0.26-0.47)
5-year OS (95% CI)	0.72 (0.69-0.75)	0.51 (0.46-0.56)	0.37 (0.30-0.44)	0.27 (0.17-0.38)
B: Among non-transformed patients*				
Median follow-up time	6.1 (0-13.8)	3.3 (0-10.9)	1.7 (0-10.3)	1.0 (0-9.1)
2-year OS (95% CI)	0.85 (0.82-0.87)	0.73 (0.68-0.77)	0.55 (0.47-0.62)	0.42 (0.29-0.54)
5-year OS (95% CI)	0.72 (0.70-0.75)	0.53 (0.48-0.58)	0.40 (0.31-0.47)	0.31 (0.19-0.44)
C: Among patients who received R-CHOP, BR, or R-single as 1st line				
2-year OS (95% CI)	0.86 (0.84-0.88)	0.76 (0.71-0.80)	0.54 (0.44-0.63)	0.50 (0.31-0.67)
5-year OS (95% CI)	0.76 (0.73-0.79)	0.58 (0.52-0.64)	0.43 (0.33-0.52)	0.25 (0.06-0.50)

FIGURE 6 a-c. Overall survival (OS) by systemic treatment line 1–4 among all patients diagnosed with follicular lymphoma (FL) 2007–2014 and followed through 2020 in Sweden regardless of treatment indication (A), among patients with non-transformed FL as treatment indication (B) and restricted to patients who received R-CHOP, BR, or R-single as 1st line treatment (C). Median follow-up time (since start of each treatment line) and point estimates of 2- and 5-year OS from the start of each treatment line are presented in Table 1.

cohort is interesting. This indicates that R-single might be used more broadly as first-line treatment in Sweden, compared with other countries where it is primarily chosen for low-risk, older and/or more frail patients.

The main strength of this study is the large, consecutive population-based cohort that reflects treatment choice and need for subsequent treatments in a comprehensive real-world setting. This data is useful as a reference for current and future treatment trials and constitutes a valuable complement to previously published reports based on selected patients from tertiary centres and/or included in clinical trials. A limitation is that only patients diagnosed until 2014 were included in the detailed data collection, wherefore the increase in the use of novel therapies is reflected only toward the end of the follow-up period. However, this allows for longer follow-up providing a more robust overview of the proportion of patients with FL who need 2nd- and further-line treatments. Still, it is likely that the multitude of novel targeted therapies, immunotherapies and immunomodulators now available will reshape the treatment landscape for FL [6, 26]. In addition, even though the median follow-up is almost 7 years, the follow-up beyond 1st line treatment will inevitably be shorter and later events may not be captured in the present study. Another limitation is that progression was defined as start of next treatment and a proportion of patients with FL progression may initially have been managed with WaW before the initiation of subsequent treatment.

5 | CONCLUSION

In conclusion, we demonstrate that a large proportion of patients with FL did not need treatment during the follow-up period or had lasting responses to 1st line treatment, whereas the increased number of treatment lines was associated with worse survival, regardless of transformation. Thus, patients with FL whose disease require multiple treatment lines constitute a patient group with a great clinical unmet need. Methods to identify these patients and the development of novel therapeutic approaches and sequencing of treatment to optimise remission are of high importance. The data presented in this study may function as reference data for future trials.

AUTHOR CONTRIBUTIONS

Tove Wästerlid, Caroline E. Dietrich, and Karin E. Smedby conceptualized and designed the study. Caroline E. Dietrich and Karin E. Smedby did the data collection Caroline E. Dietrich and Anna Oksanen performed all statistical analyses. Tove Wästerlid and Karin E. Smedby drafted the article. All authors took an active part in the interpretation of the results and revisions of the article. All authors have approved the final version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Study data are available upon request if in line with ethical and legal permissions.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

ETHICS STATEMENT

The study was approved by the Ethical Review Board in Stockholm, Sweden (2015-202831).

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SUPPORTING INFORMATION

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

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