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Prognostic value of tumor bulk in modern management of common lymphoma subtypes: an Australasian Lymphoma and Related Diseases Registry study

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EC, LW, CW, ZKM and EAH designed the study analysis. EC, CW, and EAH conducted the analysis and wrote the manuscript with LW. AB, BAC, GC, PDC, GPG, GH, AMJ, CST, SO, EMW and ZKM contributed to data interpretation. All authors approved the final manuscript.

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Abstract

The presence of a single large disease site or so-called tumor 'bulk' in lymphoma has been variably associated with outcomes and influenced management decisions. However, challenges arise in using bulk as a prognosticator due to varied definitions across different lymphoma subtypes but also within studies of each subtype, increased utility of positron emission tomography (PET) in decision-making and recent incorporation of novel therapies. We analyzed data from the Australasian Lymphoma Registry regarding presence and influence of bulk on outcomes and treatment decisions in six key subtypes: diffuse large B-cell (DLBCL), follicular, marginal zone, T-cell, Hodgkin (HL) and Burkitt lymphoma (BL). Of the 5090 eligible patients identified between 2016-2025, 88% had documented information on the presence of bulk (registry definition >5cm). Patients with bulk were more likely to receive systemic chemotherapy alone, and less likely to have localized treatment alone (radiotherapy and/or surgery), compared to those without bulk. Bulk was associated with inferior overall survival (OS) in DLBCL patients, and superior OS in HL patients, in the univariate analyses. Exploratory analysis using disease-specific bulk definitions from clinicians practising in Australia and New Zealand showed inferior progression-free survival in DLBCL (bulk >7.5cm) and OS in BL patients (bulk >10cm), but not other subtypes. We demonstrated real-world evidence of management heterogeneity for patients with bulk, with potential prognostic implications. International standardization of the definition of bulk is urged for uniform utility in PET-based and molecular prognostication across clinical studies. Trial registration at the Australian New Zealand Clinical Trials Registry: ANZCTRN12617000050358.

Introduction

The measure of lymphoma tumor burden at time of diagnosis, and specifically the presence of a single large disease site or so-called tumor 'bulk' has, for decades, been incorporated into both prognostication and treatment decision making across multiple lymphoma subtypes.[1-6] Bulk has proven prognostic value in historical studies of T-cell lymphoma (TCL) and follicular lymphoma (FL).[2, 7] Bulk is associated with local treatment failure in early diffuse large B-cell lymphoma (DLBCL) and supports treatment paradigms incorporating radiotherapy in Hodgkin Lymphoma (HL).[3, 8]

The recent advent of molecular imaging, allowing more accurate detection of metabolically active disease at baseline and post therapy, raises questions regarding the value of using bulk as part of clinical evaluation and decision-making.[9-11] In the current positron emission tomography (PET)-era, baseline bulk still dictates the management of limited-stage DLBCL, as well as early-stage HL treatment paradigms, but uncertainty arises in the use of bulk for treatment decisions relating to the added value of consolidative radiotherapy in patients with aggressive lymphoma with complete metabolic response on the post-chemotherapy PET.[11-16] In the absence of validated prognostic indices which incorporate total metabolic tumor volume and other markers of tumor burden such as circulating tumor DNA, the presence of bulk remains a relevant measure influencing the treatment of indolent lymphomas such as follicular lymphoma (FL),[17] and as a risk factor for tumor lysis syndrome (TLS) in aggressive diseases such as DLCBL and Burkitt lymphoma (BL).[18]

The use of baseline bulk in risk assessment and treatment decisions varies in clinical trials,[19] attributed to the lack of a standard definition both within and across lymphoma subtypes.[20] This variation is seen in the MabThera International Trial Group study in DLBCL examining rituximab (R) with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like chemotherapy where participating hospitals were allowed to determine their own definitions (5, 7.5, or 10cm).[3, 21] The tumor maximum diameter was used, but only a cut-off of 10cm differentiated survival differences between patients with and without bulk in the study.[3, 21] Whilst 10cm was suggested as the threshold in the R-CHOP era, the study was unable to identify an optimal cut-off between 5 to 10cm in a Martingale residual analsysis,[3, 21, 22] demonstrating the difficulty in reliably applying a single cut-off for bulk in lymphoma.

The challenge of measuring bulk consistently and employing its presence as an independent risk tool is reflected in the absence of bulk as a risk factor from the majority of modern validated prognostic indices whereby a combination of baseline clinical factors are utilized to stratify risk in lymphoma patients.[4, 6, 19, 23-31] The common DLBCL and FL prognostic scores do not incorporate bulk, including the International Prognostic Index (IPI),[32] revised IPI (R-IPI),[25] and National Comprehensive Cancer Network IPI,[33] Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2.[6, 26] Variations in data coding led to incomplete data regarding FL bulk precluding its inclusion as a potential variable in models.[6, 26]

Large contemporary, real-world analyses are lacking to understand the characteristics of those patients presenting with disease bulk, its value in prognostication and utility in treatment decisions made by clinicians in routine care.

Herein, we explore the presence of disease bulk in patients with lymphoma, with a focus on the prognostic value and influence on treatment decisions in Australian and New Zealand patients within the prospective Lymphoma and Related Diseases Registry (LaRDR).

Methods

In this multicenter registry study, newly diagnosed lymphoma patients aged ≥18 years were identified from the LaRDR. It is a clinical quality registry with 37 hospital sites, including tertiary and

regional centers, across Australia and New Zealand. Detailed methodology of the LaRDR was previously published. [34] We included DLBCL, FL, marginal zone lymphoma (MZL), peripheral TCL, HL, and BL, according to the WHO Classifications 4th or revised editions captured at the time of data collection. [35, 36]. Primary mediastinal B-cell, mantle cell, and nodular lymphocyte-predominant Hodgkin lymphomas were excluded due to limited sample size. For analyses relevant to treatment type and outcome, patients on active surveillance alone (i.e. "watch and wait") were excluded. Chronic lymphocytic leukemia/small lymphocytic lymphoma and cutaneous TCL patients were excluded from the analyses due to data unavailability in LaRDR.

2.1 Definition of bulk

For our primary analysis, we extracted the presence of bulk, a single dimension of >5cm for all disease subtypes, as defined by the LaRDR.[34] The low threshold of 5cm, along with the exact measurements were collected by the LaRDR to increase data capture due to large variations of cut-offs in different lymphoma subtypes.[19] Due to discrepancies in the published definitions of bulk,[9, 20, 37-43] we conducted exploratory analyses to evaluate the extent to which a different definition would affect the treatment selections, PFS and OS of each lymphoma subtype.[44] The most commonly used disease-specific bulk definitions identified on a survey of registry-affiliated clinicians were used. Provided options in this survey included 3cm, 5cm, 7cm, 7.5cm, 10cm, one-third mediastinal mass ratio, or unknown across the lymphoma subtypes. Data on bulk diameter were categorized into groups according to the most frequently chosen cut-off for outcome analyses.

2.2 Data collection

Data extracted were patient demographics, disease characteristics including serum lactate dehydrogenase (LDH), B symptoms, extra-nodal involvement, staging, bulk (yes/no), maximum single dimension of bulk, and treatment protocols. R-IPI for DLBCL, FLIPI, MZL IPI and Hasenclever international prognostic score (IPS) were derived.[30, 31, 45, 46] Frontline treatment selections were categorized into systemic therapy only, systemic therapy with consolidative radiotherapy, or localized treatment such as radiotherapy and/or surgical resection and/or *Helicobacter pylori* eradication therapy for gastric MZL patients. Systemic therapy including chemotherapy and/or immunotherapy (e.g. rituximab) were collected. Given significant regulatory restrictions in accessing chimeric antigen receptor T-cell therapy and bispecific therapy in Australia and New Zealand, particularly during the period of this analysis, these were not available as options. Intensity for each therapeutic regimen delivered was categorized into low, standard, or high by consensus from the LaRDR investigators (Supplementary Table S1). Treatment responses reported include assessments by PET, computed tomography (CT), or PET-CT as collected by LaRDR.

2.3 Statistical analyses

Patient characteristics, treatment selections and regimen intensity were described. Categorical variables were described in frequencies and percentages and compared using the chi-squared test. Continuous variables were described with medians and ranges. We explicitly reported the number of evaluable records for each field. We performed Kaplan-Meier analyses on progression-free survival (PFS) and overall survival (OS), and log-rank test in the treated cohort for p-values. PFS was defined as time from commencement of treatment to progression, relapse or death, while OS was defined as the interval from diagnosis to death from any cause. Hazard ratios (HR) were determined using Cox regression. Stage-specific analyses were applied to the HL patients as aligned with modern treatment paradigm regarding radiotherapy use, and risk stratification by bulk in clinical practice. Multivariate analyses on bulk, which applied to both 5cm and survey-defined cut-offs in the exploratory analysis, were conducted for DLBCL, FL and HL using disease-specific and validated prognostic indices. All analyses were conducted in Stata v17 (StatCorp LLC, College Station, TX).

This analysis is within the scope of the LaRDR protocol ethically approved by the Monash Health Human Research Ethics Committee (HREC/16/MonH/74).

Results

5090 patients recruited to LaRDR from 37 participating sites between 1 January 2016 and 3 January 2025 were included. Median follow-up was 23.5 months.

3.1 Bulky disease

Presence of bulk according to the standardized LaRDR definition (>5cm) was reported in 27.0% (1372/5090) of patients with available data (Table 1). Data on bulk were missing in 12.4% of the overall cohort and the rates differed across lymphoma subtypes (p=0.003) with the rate highest in MZL (16.4%) and lowest in BL (4.8%) (Table 1).

The maximum dimension of bulk in a single site was reported in 86.7% (1189/1372) of cases (Table 2). Of these, 36.2% (431/1189) had a diameter of >10cm (8.5% of the total cohort). The anatomical site of bulky disease was available and documented in 99% (1356/1372) of cases with 72.4% (982/1356) involving nodal areas and the remainder made up of extra-nodal sites with bone (10.8%, n=146) and gastrointestinal (5.8%, n=78) being the most common of these.

3.2 Patient characteristics

Patient characteristics according to the presence of bulk are presented (Table 2). Compared to patients without bulk, DLBCL patients with bulky disease were more likely to have advanced stage disease (p<0.001), elevated LDH (p<0.001), B symptoms (p=0.004) and higher R-IPI (p<0.001); HL patients with bulk were more likely to be younger (p<0.001); FL patients with bulk were more likely to be male (p=0.003), advanced stage disease (p<0.001), elevated LDH (p<0.001), B symptoms (p<0.001), and have higher FLIPI (p<0.001); TCL and MZL patients with bulk were likely to have both advanced stage disease (p=0.011; p=0.002) and B symptoms (p=0.026; p=0.040).

3.3 Treatment selections

In patients who commenced any therapy, choice of frontline treatment employed was analyzed according to presence of bulk (Table 3). Compared to patients who did not present with bulk in the whole study cohort (p<0.001), patients with bulk were more likely to receive systemic chemotherapy alone, and less likely to have localized treatment alone. DLBCL patients with bulk were less likely to receive systemic chemotherapy alone, but more likely to receive chemotherapy with consolidative radiotherapy (p=0.017); FL and MZL patients with bulk were more likely to receive systemic chemotherapy alone, and less likely to receive localized treatment alone, (p<0.001; p=0.010, respectively).

3.4 Local radiotherapy and response assessment

Of the patients who received local radiotherapy alone (aggressive lymphoma=27, indolent=221), there was no association between the presence of bulk and the aggressiveness of the lymphomas (p=0.40). No difference in the end-of-treatment response from radiotherapy was found between patients with or without bulk (p=0.53). Of the 29 patients who received local radiotherapy and were assessed by PET, 33.3% had bulk compared to 11.4% without bulk (p=0.002).

3.5 Systemic therapy treatment intensity

Presence of bulky disease in HL patients was associated with a higher likelihood of receiving systemic chemotherapy in high intensity, compared to those without bulk (22.3% versus 14.9%, respectively, p=0.047). No variations in the intensity of systemic chemotherapy were observed in patients in other lymphoma subtypes (Figure 2).

3.6 Survival outcomes

Using the registry-defined presence of bulk, inferior OS was observed in DLBCL patients with bulk (HR=1.26, 95% confidence interval [CI]=1.05–1.50, p=0.011, Figure 1B).

In all-stage HL patients, superior OS was observed in those with bulky disease, compared to those without bulk (HR=0.28, 95% CI=0.11–0.73, p=0.009, Figure 1F). This OS difference in HL patients did not persist when restricted the subgroup analyses by staging: early (HR not evaluable) or advanced stage disease (HR=0.39, 95% CI=0.15–1.02, p=0.056) cohorts. When adjusting for IPS, the OS of HL patients with bulk remained superior (adjusted HR=0.25, 95%CI=0.10–0.64, p=0.004). However, when we further adjusted for IPS and age as a continuous variable, due to the strong association between age and bulky disease observed in Table 2, the difference in OS of HL patients was no longer sustained (adjusted HR=0.50, 95% CI=0.16-1.54, p=0.23) (Table 4). The presence of bulk was not associated with any OS differences for FL (Figure 1D), MZL, TCL, or BL (Table 4, Supplementary Figure S1). Of note, the Kaplan-Meier curve for MZL showed a weak significant difference (Supplementary Figure S1E), but the estimate was not confirmed by the cox proportional model where the confidence intervals overlapped null (HR=2.04, 95% CI=1.00-4.15), likely due to insufficient statistical power.

Statistical differences in PFS according to presence of bulk was only found in DLBCL (HR=1.27, 95%CI=1.07–1.50, p=0.007) (Figure 1A, Table 4, Supplementary Figure S1) and not in FL (Figure 1C) or HL (Figure 1E).

3.7 Exploratory analysis

In the 56 participating clinicians, the most common definitions of bulk used for each subtype were: FL, 7cm; DLBCL, TCL and MZL, 7.5cm; HL and BL, 10cm (Supplementary Figure S2). Although both 7.5cm and 10cm were equally common selections for BL, we used 10cm as this aligned with published literature.[47, 48]

Analyses of the relationship between our survey-defined bulk and treatment selections for each disease subtype are described (Supplementary Table S2). Differences between bulky and non-bulky disease cohorts in treatment selections were observed in FL (n=232) using 7cm cut-off and MZL (n=38) using 7.5cm cut-off. Using these definitions of bulk, FL and MZL patients who had bulk and commenced treatments were more likely to have systemic chemotherapy only, and less likely to have local treatment alone, compared to those did not (p<0.001; p=0.007, respectively).

When using survey-defined bulk cut-off, only inferior OS in BL (10cm) and inferior PFS in DLBCL (7.5cm) were found among all subtypes. However, upon adjusting for prognostic indices for DLBCL, HL and FL, the significant difference on PFS in DLBCL did not persist (Supplementary Table S3). To further investigate if there was an optimal definition bulk for survival prognostication, we generated HR for OS using the different size definitions of bulk employed by our three largest groups of lymphoma patients (DLBCL, FL and HL). Although the unadjusted HRs for HL were demonstrating significant differences, the overlapping estimates indicated that no individual definitions were the optimal cut-off (Supplementary Table S4).

Discussion

This is the first registry analysis reporting the outcomes of tumor bulk in patients with six key subtypes of lymphoma. We found the presence of tumor bulk was associated with inferior PFS and OS in DLBCL, and superior OS in HL in the univariate analyses; however, only the difference of PFS in DLBCL was sustained in the multivariate analyses adjusting for prognostic indices. Compared to those without bulky disease, indolent lymphoma patients with bulk were less likely to receive local

treatment alone; DLBCL patients with bulk were more likely to receive chemotherapy with consolidative radiotherapy; and HL patients with bulk were more likely to receive high intensity systemic chemotherapy.

The inferior OS of DLBCL patients with bulky disease in our cohort was consistent with those in the MabThera International Trial Group study who also received CHOP-like regimens.[37] The superior OS in our all-stage HL cohort in the univariate analysis was similar to a multicenter study of advanced-stage HL patients with bulky disease (≥5cm);[49] further analysis of our advanced-stage HL was limited by the small sample size.

Associations between presence of bulk and frontline treatment selections were found in the overall cohort when using a pan-lymphoma definition (5cm), and specifically in FL (7cm) and MZL (7.5cm) with the disease-based definitions. These indolent lymphoma data align with the Group d' Etude des Lymphomes Folliculaires criteria recommendations,[17] commencing treatment due to high tumor burden (7cm). Mandated national guidelines on lymphoma diagnosis and treatments were not available in Australia and New Zealand, although recommendations from local expert group were published to guide clinical practice.[50-54] Among those, tumor bulk was mentioned in DLBCL.[52] Future analyses to evaluate practice adherence to the consensus guidelines could be insightful in revealing the potential reasons for the choice of tumor bulk definitions.

We were able to assess bulk using one unified definition across the cases (5cm) and also the disease-based definitions identified by clinicians. In the exploratory analyses using the survey-defined cut-offs on the single maximum dimensions collected by the LaRDR, OS differences in HL (10cm) were no longer observed whereas OS for BL (10cm) became inferior. The PFS difference for DLBCL (7.5cm), however, was sustained. The sample size in the exploratory analyses was restricted by the availability of the maximum dimensions, which may have led to these varied findings. Nonetheless, the heterogeneity in observed outcomes suggests prognostic significance between bulky disease and its definitions. We welcome international collaboration to undertake further evaluation to inform a data-driven consensus for definitions of bulk. Forming a larger patient cohort from international registry datasets will also allow validation of our findings.

Similar to our exploratory analysis in DLBCL, extranodal disease bulk (7.5cm) was prognostic for PFS in a Korean clinical trial of patients with bulky DLBCL receiving R-CHOP.[55] Further subgroup analysis by nodal or extranodal bulk was unavailable in our study because the reported bulky disease was pre-defined by the LaRDR participating hospitals. As for our HL cohort, the OS differences did not persist using a 10cm cut-off, contrary to a multicenter retrospective study suggesting a U-shaped relationship between bulk and superior OS pivoting at 10cm.[49] Future studies concentrating on the prognosis of HL would be desirable as long-term follow-up data become available.

We are limited in the small sample sizes of subgroups such as the rarer lymphomas in our cohort, and relatively short follow-up data for patients with indolent lymphoma, potentially reducing the statistical power. In particular, the sample size for TCL, MZL and BL were too small to perform multivariate analyses to assess the true effect of tumor bulk on prognosis. Infrastructure to centrally collect measurements of bulky disease with graphics representations, interim PET scans, TLS, and indication for regimen choice was unavailable in LaRDR. In addition, the absence of a standardized timepoint for performing interim PETs in the Australian and New Zealand clinical practice precludes its inclusion in the results. Furthermore, we noted variability in rates of missing data according to histology and specific diameters of largest lesions were missing in 13% of overall cases, suggesting the challenges of obtaining accurate data in routine care. Potential variation in using a standard measure of bulk by unidimensional parameters in trials may be reflected in clinical practice,[56] and this variation extends to different LaRDR participating sites and individual radiologists. Other

limitations of registry data include the difficulties in determining how sites determined the definition of bulky disease (as bulky disease is a binary yes/no option and the size of the largest node provided), whether the presence of extra-nodal disease dictated or contributed to decision to treat or the reasons for clinician decision in choosing particular treatment paradigms. Finally, the inclusion of localized therapy cohort was to provide an accurate representation of real-world patients though noting that localized therapy itself may not be standard of care for certain lymphomas, particularly the aggressive subtypes.

While our study focuses on the absolute size of bulk, we do recognize from a clinical perspective, the associated disease and location of bulk, rather than the threshold, can also be significant in dictating treatments and anticipating complications. Superior vena cava obstruction, airway compromise and nerve impingements are often presenting symptoms of large HLs. BL and other high-grade B-cell lymphomas confer a risk of perforation at extra-nodal sites such as the gastrointestinal tract given their propensity for rapid proliferative invasion. Additionally, in SMZL, treatment is indicated from clinical symptom burden of bulk rather than a pre-defined threshold.

The choice to focus on survival outcomes such as PFS or OS rather than response to treatment (while appreciating this is key determinant of outcomes), relates to the latter being heavily impacted or confounded by treatment-specific factors (including intensity of regimen, deliverability and timing of imaging post therapy). Survival outcomes may reflect more stable indicators of baseline prognosis. Bulk did not demonstrate independent prognostic value in our study in a multivariate analysis with other baseline features, therefore we have avoided including other variables that are heavily influenced by treatment (such as disease-free intervals, intensity of treatment, disease response). This is partly due to the registry not collecting robust data on reasons for particular treatment paradigms, which can influence response as mentioned earlier.

The uncertainties in determining the parameters for bulk assessment, and its values in prognostication and treatment decisions continue to challenge the clinical trials which rely on tumor burden as a measure of disease, stratification and enrolment. Other measures of tumor burden such as novel PET metrics,[9] harnessing artificial intelligence and genomic techniques, likewise are challenged by the lack of validated algorithms and standard definitions.

In summary, we found associations between tumor bulk and outcomes in DLBCL and all-stage HL cohorts using a pan-lymphoma definition of bulk (>5cm) in the univariate analyses, but these did not retain significance in multivariate testing. The presence of bulk was associated with greater use of systemic treatment and lesser use of localized treatment alone in the study cohort, but did not influence the intensity of chosen regimen except in HL. Clinical use of bulky disease in management approaches is more consistent with international guidelines in indolent lymphoma compared to other subtypes with respect to definition and treatment choice. The presence, or absence of bulk, and its definition are fraught with high variation in the contributing factors. Thus, determining the optimal definition of disease bulk for each subtype, the associations with underlying biology, and evaluating the utility of this metric in the modern PET era, are priorities for future research.

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Table 1 Details of bulk in all patients and each disease subtype.

		Aggressive lymphoma				Indolent lymphoma	
	All patients	DLBCL	TCL	HL*	BL	FL	MZL
N evaluable	5090	2197	365	799	83	1164	482
Bulk							
No (%)	3088 (61)	1204 (55)	272 (75)	448 (56)	54 (65)	761 (65)	349 (73)
Yes (%)	1372 (27)	710 (32)	49 (13)	248 (31)	25 (30)	286 (25)	54 (11)
Unknown (%)	630 (12)	283 (13)	44 (12)	103 (13)	4 (5)	117 (10)	79 (16)
N maximum single dimension of largest lesion entered into LaRDR, (%)	1189 (87)	611 (81)	43 (88)	210 (85)	22 (88)	260 (91)	43 (80)
Median maximum single dimension (cm), (range)	9 (1-27)	9 (1-27)	8 (5-22)	9 (4-23)	8 (5-15)	9 (5-26)	9 (5-26)
Maximum single dimension (cm), (%)							
>5cm	1159 (98)	596 (98)	40 (93)	204 (97)	22 (100)	257 (99)	40 (93)
>7cm	803 (59)	418 (68)	27 (63)	141 (67)	14 (64)	176 (68)	27 (63)
>7.5cm	747 (55)	392 (64)	27 (63)	126 (60)	12 (55)	165 (64)	25 (58)
>10cm	431 (31)	226 (37)	17 (40)	69 (33)	9 (41)	91 (35)	19 (44)

DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma.

* HL mediastinal mass ratio (MMR) is not collected by LaRDR so cannot be reported despite being recognized as a component of the definition of bulk determined by clinicians.

Table 2 Patient characteristics according to presence of bulk in each disease subtype.

	All patients		Aggressive lymphoma								Indolent lymphoma			
			DLBCL		TCL		HL		BL		FL		MZL	
N evaluable	4460		1914		321		696		79		1047		403	
Bulk	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
	3088	1372	1204	710	272	49	448	248	54	25	761	286	349	54
Median age (range)	**65**	**63**	69	68	62	62	**41**	**31**	49	56	65	65	67	70
	(18-103)	**(18-99)**	(20-103)	(22-99)	(18-93)	(24-87)	**(18-93)**	**(18-88)**	(19-82)	(18-88)	(25-91)	(35-98)	(28-96)	(39-90)
Male sex (%)	**1688**	**821**	676	424	164	33	257	137	41	18	**396**	**178**	155	31
	(55)	**(60)**	(56)	(60)	(60)	(67)	(58)	(55)	(76)	(72)	**(52)**	**(62)**	(44)	(57)
Stage III-IV (%)	**1726**	**896**	**715**	**480**	**166**	**39**	227	110	27	15	**458**	**219**	**133**	**33**
	(60)	**(68)**	**(63)**	**(71)**	**(70)**	**(89)**	(52)	(46)	(59)	(68)	**(64)**	**(79)**	**(47)**	**(72)**
Elevated LDH (%)	**1040**	**687**	**552**	**442**	133	31	-	-	31	18	**133**	**82**	78	10
	(41)	**(57)**	**(54)**	**(71)**	(59)	(69)			(61)	(82)	**(21)**	**(32)**	(29)	(25)
B symptoms (%)	**732**	**459**	**239**	**189**	**102**	**26**	159	109	13	10	**107**	**77**	**46**	**13**
	(25)	**(35)**	**(26)**	**(34)**	**(40)**	**(58)**	(37)	(45)	(26)	(46)	**(15)**	**(28)**	**(14)**	**(26)**
Extranodal involvement (%)	1820	864	828	511	196	35	173	104	39	19	321	158	264	37
	(59)	(63)	(69)	(72)	(72)	(71)	(39)	(42)	(70)	(76)	(42)	(55)	(76)	(69)
Risk score														
Low	-	-	**82 (9)**	**22 (4)**	-	-	242 (57)	143 (61)	-	-	**250 (42)**	**62 (25)**	126 (48)	13 (33)
Intermediate	-	-	**381 (42)**	**224 (40)**	-	-	145 (34)	67 (29)	-	-	**206 (35)**	**82 (33)**	128 (48)	24 (60)
High	-	-	**437 (49)**	**310 (56)**	-	-	39 (9)	25 (11)	-	-	**139 (23)**	**103 (42)**	11 (4)	3 (8)

DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma.

Bold font denotes statistically significant difference ($p \leq 0.05$).

Table 3 Frontline treatment selection according to presence of bulk in each disease subtype.

	All patients		Aggressive lymphoma								Indolent lymphoma									
			DLBCL		TCL		HL		BL		FL		MZL†							
															SMZL		MALT		NMZL	
N evaluable	3872		1805		296		666		76		741		288		57		135		96	
Bulk (5cm)	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
	2579	1293	1128	677	250	46	426	240	51	25	484	257	240	48	53	4	119	16	68	28
Treatment categories																				
Systemic chemotherapy only	**2070**	**1101**	**999**	**568**	205	43	333	203	51	25	**348**	**224**	**134**	**38**	47	3	39	10	48	25
	(80)	**(85)**	**(89)**	**(84)**	(82)	(94)	(78)	(85)	(100)	(100)	**(72)**	**(87)**	**(56)**	**(79)**	(89)	(75)	(33)	(63)	(71)	(89)
Chemotherapy with	**259**	**150**	**117**	**100**	22	3	89	36	0 (0)	0 (0)	**27**	**11**	**4**	**0**	0	0 (0)	2	0 (0)	2	0 (0)
consolidative radiotherapy	**(10)**	**(12)**	**(10)**	**(15)**	(9)	(7)	(21)	(15)			**(6)**	**(4)**	**(2)**	**(0)**	(0)		(2)		(3)	
Localized treatment*	**250**	**42**	**12**	**9**	23	0	4	1	0 (0)	0 (0)	**109**	**22**	**102**	**10**	6	1 (25)	78	6	18	3
	(10)	**(3)**	**(1)**	**(1)**	(9)	(0)	(1)	(<1)			**(23)**	**(9)**	**(43)**	**(21)**	(11)		(65)	(37)	(28)	(11)

DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NMZL: nodal marginal zone lymphoma.

Bold font denotes statistically significant difference ($p \leq 0.05$).

*Local treatment includes surgical excision, localized radiotherapy, and *Helicobacter pylori* eradication therapy for gastric marginal zone lymphoma patients.

† Further details of the subtypes of marginal zone lymphoma (SMZL, MALT, and NMZL) were provided in the table.

Table 4 Hazard ratios of PFS and OS according to bulk in all patients and each disease subtype.

	All patients	Aggressive lymphoma				Indolent lymphoma	
		DLBCL	TCL	HL	BL	FL	MZL
Bulk (5cm)							
PFS (95% CI)	1.07	**1.27**	1.07	0.92	1.73	0.94	1.26
	(0.94 – 1.22)	**(1.07 – 1.50)**	(0.73 – 1.58)	(0.59 – 1.43)	(0.56 – 5.31)	(0.67 – 1.31)	(0.63 – 2.51)
OS (95% CI)	1.14	**1.26**	0.98	**0.28**[†]	1.73	0.94	2.04
	(0.99 – 1.31)	**(1.05 – 1.50)**	(0.64 – 1.50)	**(0.11 – 0.73)**	(0.55 – 5.45)	(0.62 – 1.43)	(1.00 – 4.15)
Bulk (5cm) adjusted for prognostic scores[*]							
PFS (95% CI)	-	**1.19**	-	0.90	-	0.87	-
		(1.00 – 1.41)		(0.58 – 1.41)		(0.62 – 1.22)	
OS (95% CI)	-	1.16	-	**0.25**	-	0.78	-
		(0.97 – 1.39)		**(0.10 – 0.64)**[‡]		(0.51 – 1.18)	

PFS: progression-free survival; OS, overall survival; CI; confidence interval; DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma.

Bold font denotes statistically significant difference ($p \leq 0.05$).

[*] Prognostic scores used in estimating hazard ratios: DLBCL, RIPI; FL, FLIPI; HL, Hasenclever international prognostic score.

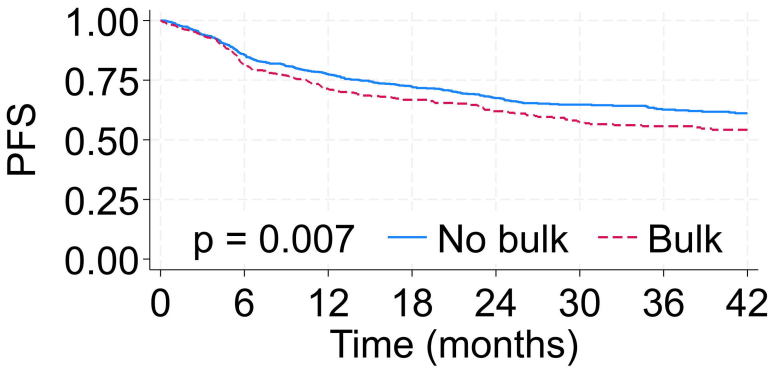
[†] There was no difference when analyzing the OS in bulk versus non-bulky groups of HL in early or advanced stages in HL.

[‡] There was no difference when adjusting for Hasenclever international prognostic score and age as a continuous variable.

Figure 1. Survival outcomes of the patients according to the presence of bulky disease. (A) PFS of DLBCL. (B) OS of DLBCL. (C) PFS of FL. (D) OS of FL. (E) PFS of HL. (F) OS of HL. PFS: progression-free survival; OS: overall survival; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma.

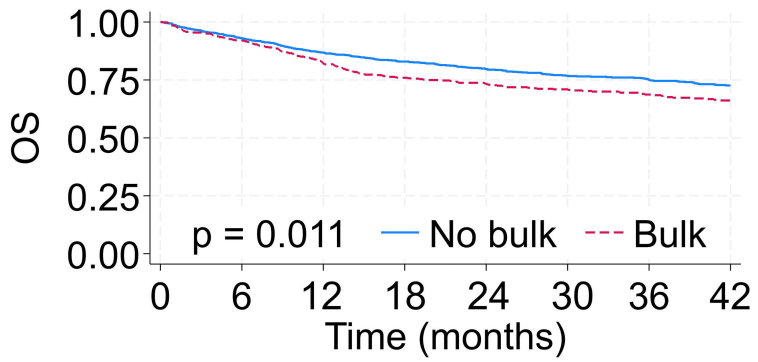
Figure 2. Systemic therapy treatment intensity according to presence of bulk in each disease subtype. DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma.

A



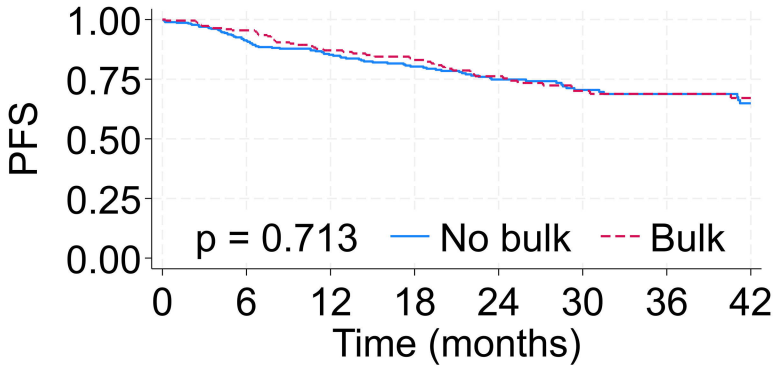
At risk								
No bulk	1027	775	582	482	371	280	228	182
Bulk	615	442	313	256	199	148	118	101

B



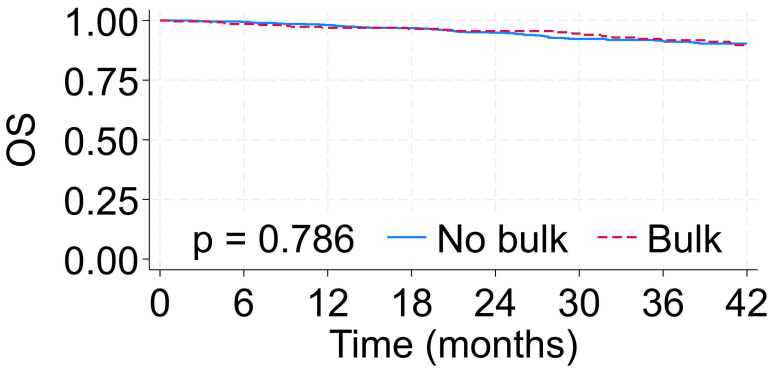
At risk								
No bulk	1179	997	828	708	625	528	458	387
Bulk	699	582	466	388	352	302	255	221

C



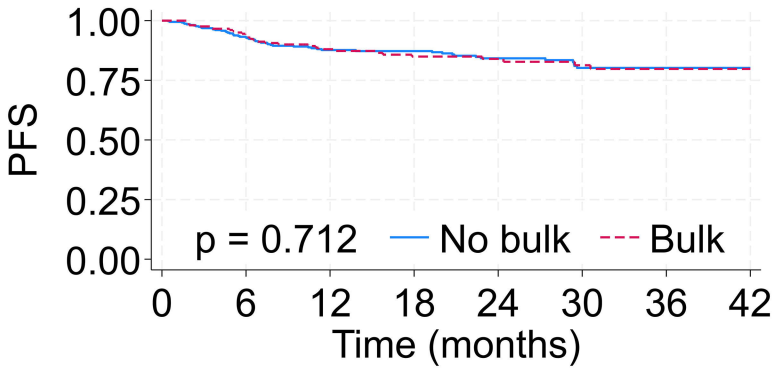
At risk								
No bulk	364	294	222	181	125	90	65	48
Bulk	228	199	144	116	86	59	46	38

D



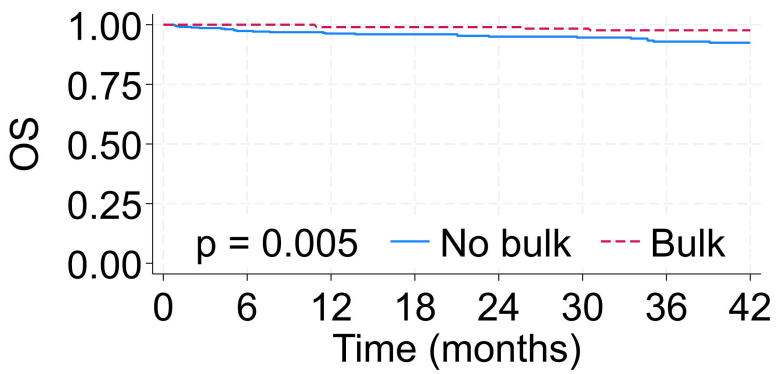
At risk								
No bulk	734	690	624	576	517	434	374	320
Bulk	280	259	236	216	198	177	159	128

E

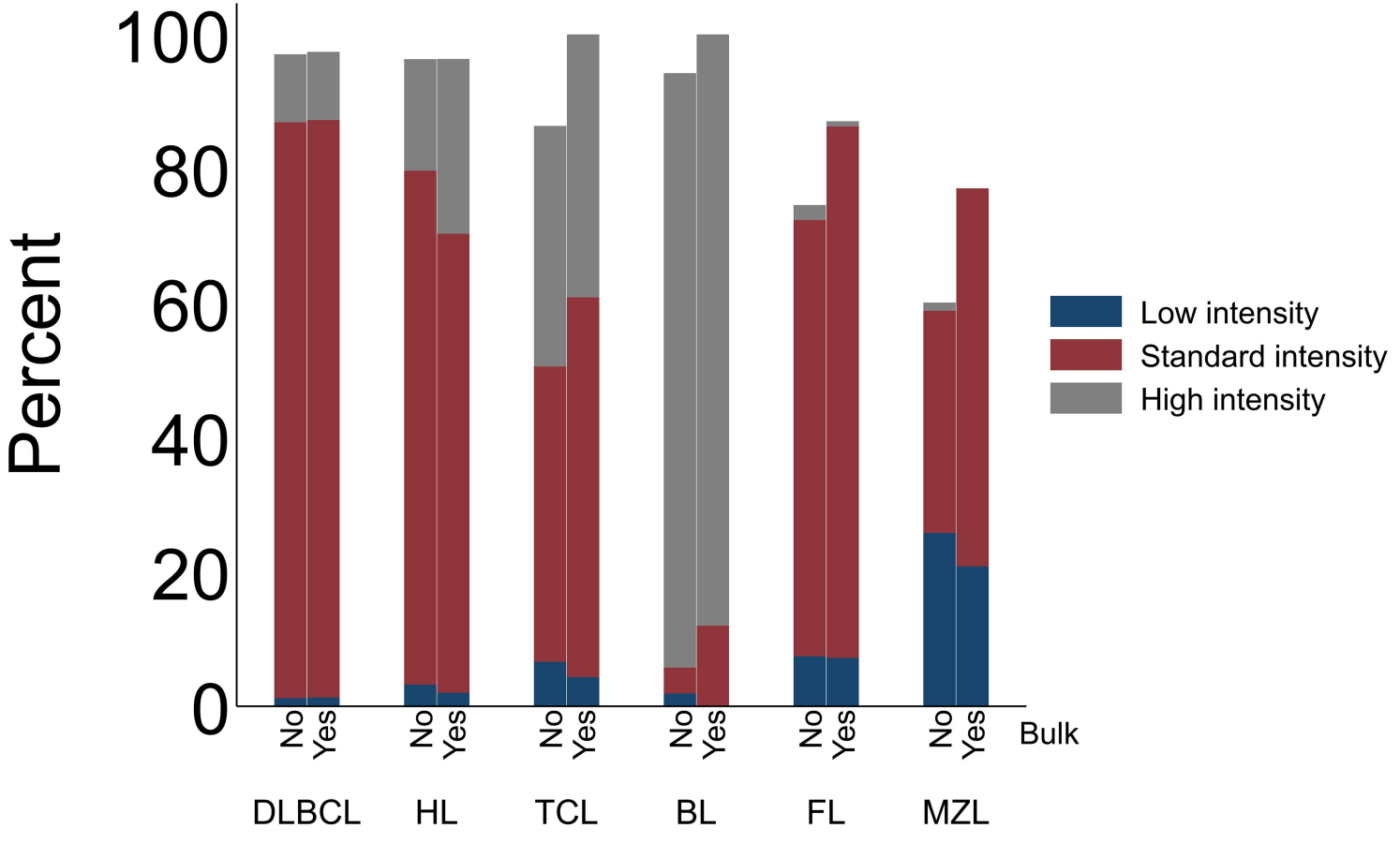


At risk								
No bulk	386	306	216	189	131	98	81	69
Bulk	216	174	125	106	74	55	44	35

F



At risk								
No bulk	434	390	336	308	273	241	210	184
Bulk	245	214	191	181	163	143	122	101


Percent
100
80
60
40
20
0
No
Yes
Bulk
DLBCL
HL
TCL
BL
FL
MZL
Low intensity
Standard intensity
High intensity

Supplementary Appendix

Supplementary Table S1. Lymphoma treatment regimens from the LaRDR according to intensity.

Low intensity
(R) Gemcitabine and vinORELBine
Brentuximab Vedotin
Chlorambucil and Rituximab
ChlVPP (Chlorambucil vinBLASTine Procarbazine Prednisolone)
Ibrutinib
PVAG (Prednisolone vinBLASTine DOXOrubicin Gemcitabine)
Rituximab monotherapy
VinCRISTine
Standard intensity
(R) ICE (Fractionated or infused IFOSFamide cARBOplatin Etoposide +/-rituximab)
(R) GDP (Gemcitabine Dexamethasone cISplatin)
(R)-CHOP21
ABVD (DOXOrubicin Bleomycin VinBLASTine Dacarbazine)-like
Bendamustine and RITUximab
R-CEOP (Rituximab, Cyclophosphamide, Etoposide Phosphate, Vincristine, Prednisolone)
R-CHEP (Rituximab / Cyclophosphamide / Doxorubicin / Etoposide Phosphate / Prednisolone)
R-CVP (RITUximab CYCLOPHOSPHamide vinCRISTine Prednisolone)
R-DHAP (RITUximab Dexamethasone Cytarabine cISplatin)
R-GCVP (Rituximab Gemcitabine Cyclophosphamide Vincristine and Prednisolone)
R-GemOX (RITUximab Gemcitabine Oxaliplatin)
R-miniCHOP (rituximab combined with low-dose CHOP)
R-MPV (RITUximab, Methotrexate, Procarbazine, and Vincristine)
High intensity
(R) CHOEP21 (rituximab, CYCLOPHOSPHamide DOXOrubicin vinCRISTine Etoposide Prednisolone)
(R)-CHOP14 (CYCLOPHOSPHamide DOXOrubicin vinCRISTine Prednisolone)
BEACOPP Escalated (Bleomycin Etoposide DOXOrubicin CYCLOPHOSPHamide VinCRISTine Procarbazine Prednisolone)
DA-R-EPOCH (Dose Adjusted RITUximab Etoposide Prednisolone vinCRISTine CYCLOPHOSPHamide DOXOrubicin)
ESHAP (Etoposide Methylprednisolone Cytarabine cISplatin)
Hyper CVAD Part A and B
IVAC (iFOSFamide etoposide cytarabine) followed by Cy-TBI

R-CHOEP14
R-CODOX-M +/-IVAC (Rituximab, CYCLOPHOSPHamide vinCRISTine DOXOrubicin Methotrexate, IFOSFamide Etoposide Cytarabine)
R-maxi-CHOP and R-HiDAC Treatment
SMARTE-R-CHOP14 (RITUximab CYCLOPHOSPHamide DOXOrubicin VinCRISTine Prednisolone)
SMILE (Dexamethasone Methotrexate IFOSFamide L-asparaginase Etoposide)

Supplementary Table S2. Frontline treatment selection according to presence of bulk as defined by survey in each disease subtype.

	Aggressive lymphoma								**Indolent lymphoma**									
	DLBCL (7.5cm)		**TCL (7.5cm)**		**HL (10cm)**		**BL (7.5cm)**		**FL (7cm)**		**MZL (7.5cm)**		**SMZL***		**MALT**		**NMZL**	
N evaluable in exploratory analysis	584		34		202		21		232		38		-	-	13		22	
Bulk	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	-	-	N	Y	N	Y
	208	376	14	26	137	65	13	9	67	165	15	23			8	5	6	16
Treatment categories																		
Systemic chemotherapy only	177 (85)	307 (82)	14 (100)	23 (88)	118 (87)	52 (80)	13 (100)	9 (100)	**52 (78)**	**151 (92)**	**8 (53)**	**21 (91)**	-	-	3 (38)	4 (80)	4 (67)	15 (94)
Chemotherapy with consolidative radiotherapy	28 (14)	64 (17)	0 (0)	3 (12)	18 (13)	13 (20)	0 (0)	0 (0)	**2 (3)**	**7 (4)**	**0 (0)**	**0 (0)**	-	-	0 (0)	0 (0)	0 (0)	0 (0)
Localized treatment†	3 (<1)	3 (1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	**13 (19)**	**7 (4)**	**7 (47)**	**2 (9)**	-	-	5 (62)	1 (20)	2 (33)	1 (6)

DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; MALT: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NMZL: nodal marginal zone lymphoma.

Bold font denotes statistically significant difference ($p \leq 0.05$).

* Further details of the subtypes of marginal zone lymphoma (SMZL, MALT, and NMZL) were provided in the table. No data was available in the SMZL group by using bulk cut-off of 7.5 cm for analysis due to a small sample size.

†Local treatment includes surgical excision and/or localized radiotherapy and/or helicobacter pylori eradication therapy for gastric MZL patients.

Supplementary Table S3. Hazard ratios of PFS and OS according to bulk as defined by survey in each disease subtype.

	Aggressive lymphoma				Indolent lymphoma	
	DLBCL (>7.5cm)	**TCL (>7.5cm)**	**HL (>10cm)**	**BL (>7.5cm)**	**FL (>7cm)**	**MZL (>7.5cm)**
Bulk						
PFS (95% CI)	**1.23**	0.90	0.50	3.06	0.96	0.78
	(1.01 – 1.51)	(0.55 – 1.47)	(0.20 – 1.22)	(0.93 – 10.06)	(0.65 – 1.40)	(0.27 – 2.19)
OS (95% CI)	1.17	0.91		**3.80**	0.85	1.68
	(0.95 – 1.45)	(0.53 – 1.56)	Not evaluable†	**(1.14 – 12.63)**	(0.51 – 1.43)	(0.60 – 4.72)
Bulk adjusted for prognostic scores*						
PFS (95%CI)	1.11	-	0.54	-	0.89	-
	(0.91 – 1.36)		(0.22 – 1.35)		(0.61 – 1.30)	
OS (95%CI)	1.04	-		-	0.70	-
	(0.84 – 1.28)		Not evaluable†		(0.41 – 1.17)	

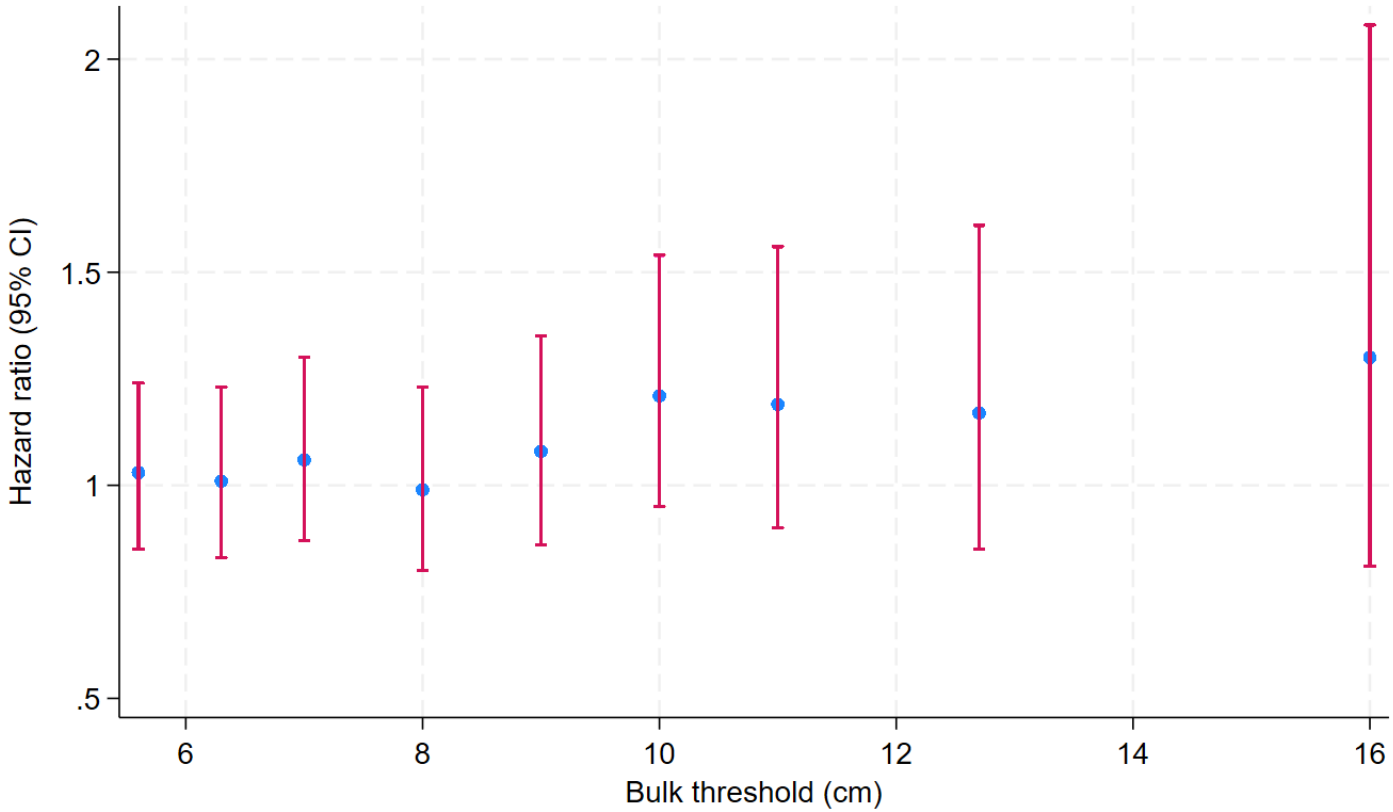
PFS: progression-free survival; OS: overall survival; CI: confiendence interval; DLBCL: diffuse large B-cell lymphoma; TCL: T-cell lymphoma; HL: Hodgkin lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma.

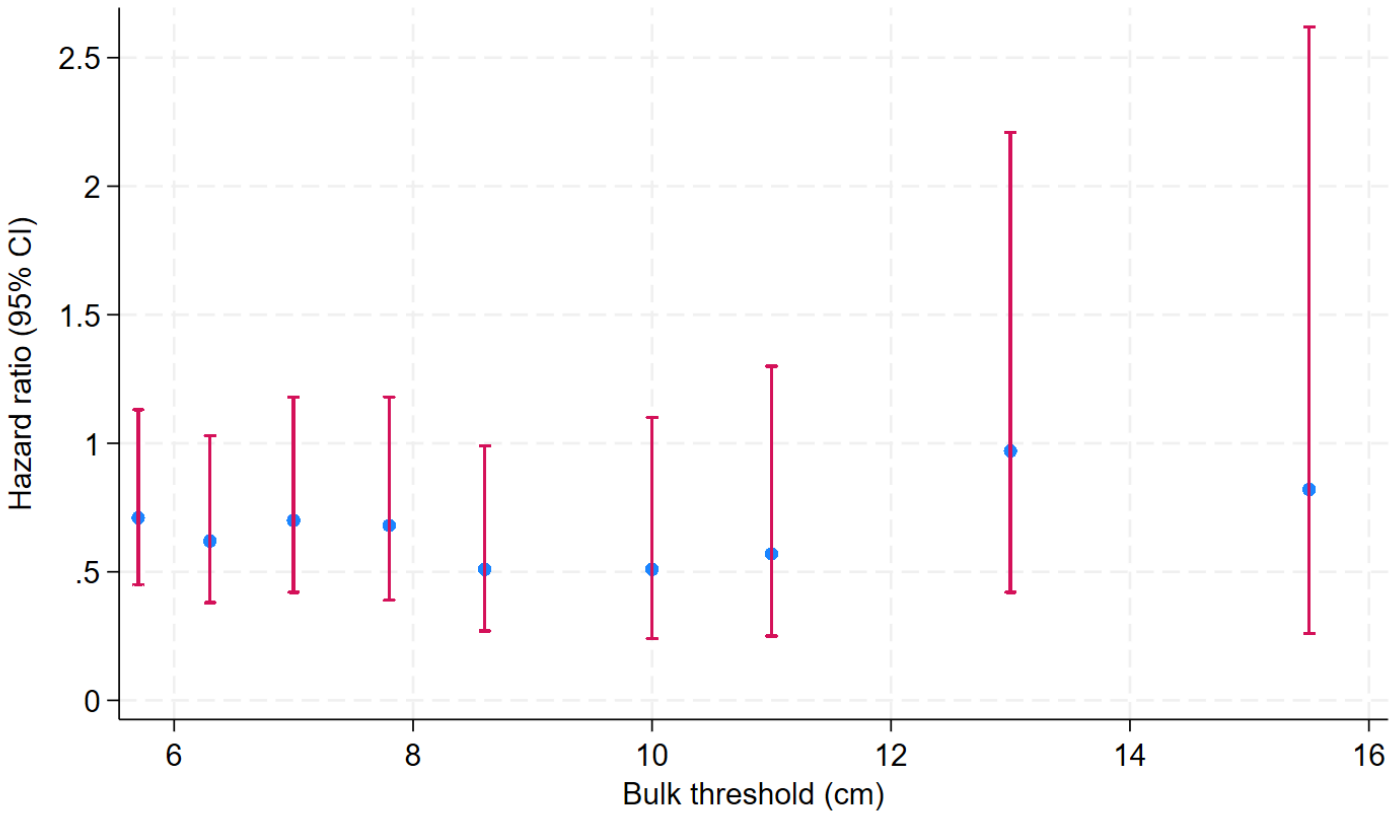
Bold font denotes statistically significant difference (p≤0.05).

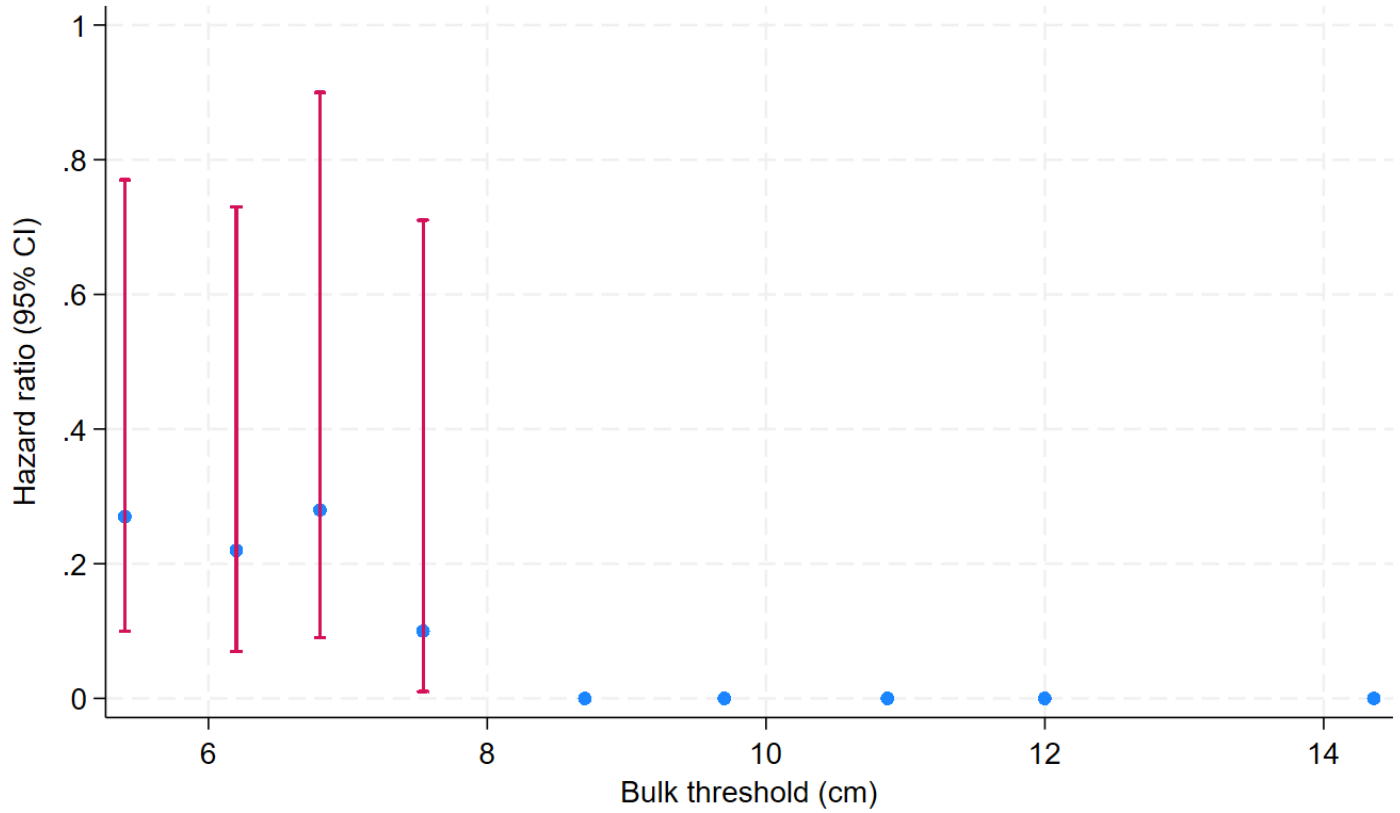
*Prognostic scores used in estimating hazard ratios: DLBCL, RIPI; FL, FLIPI; HL, Hasenclever international prognostic score.

† Overall survival of HL patients was not evaluable due to small sample size.

Supplementary Table S4. Hazard ratios of overall survival using different definitions of bulk in DLBCL, FL and HL.

Lymphoma subtypes	Number of patients with reported measurement	Hazard ratios for overall survival using different definitions of bulk
DLBCL	611	

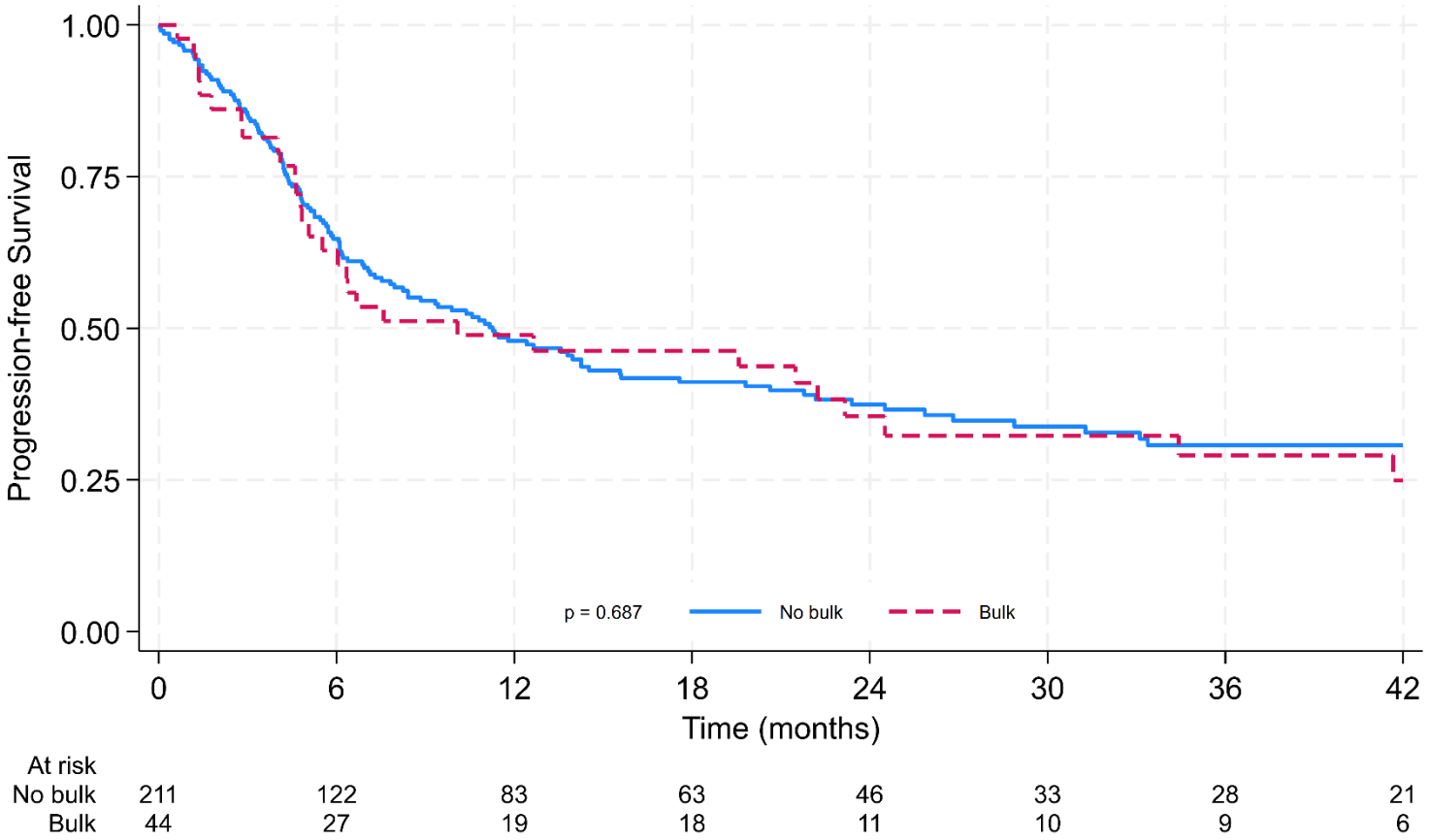
FL	260	 Hazard ratio (95% CI) 2.5 2 1.5 1 .5 0 6 8 10 12 14 16 Bulk threshold (cm)

HL	210	

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma.

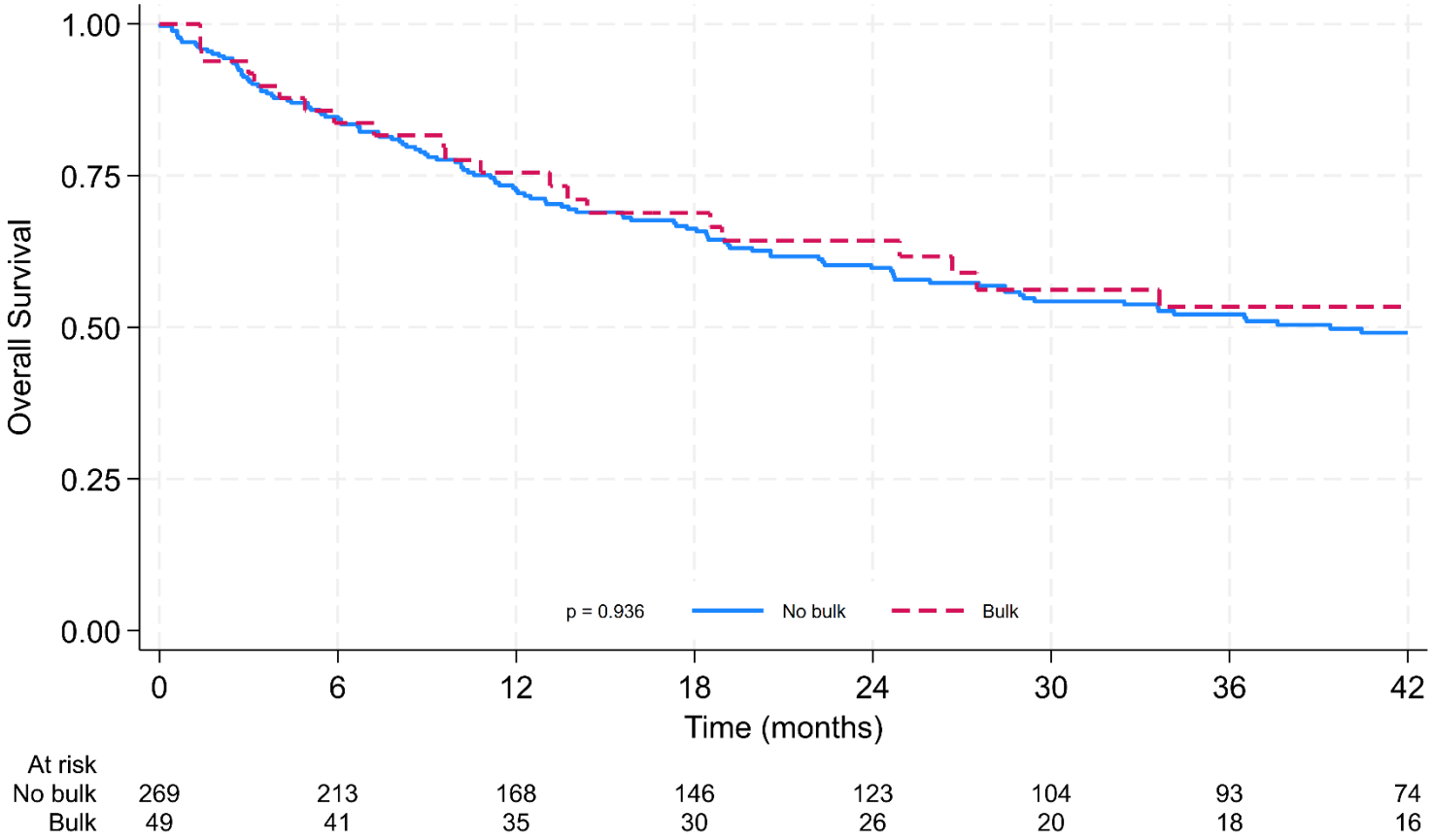
Supplementary Figure S1. Survival outcomes of the patients according to the presence of bulky disease. (A) PFS of TCL. (B) OS of TCL. (C) PFS of BL. (D) OS of BL. (E) PFS of MZL. (F) OS of MZL. PFS: progression-free survival; OS: overall survival; TCL: T-cell lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma.

(A)



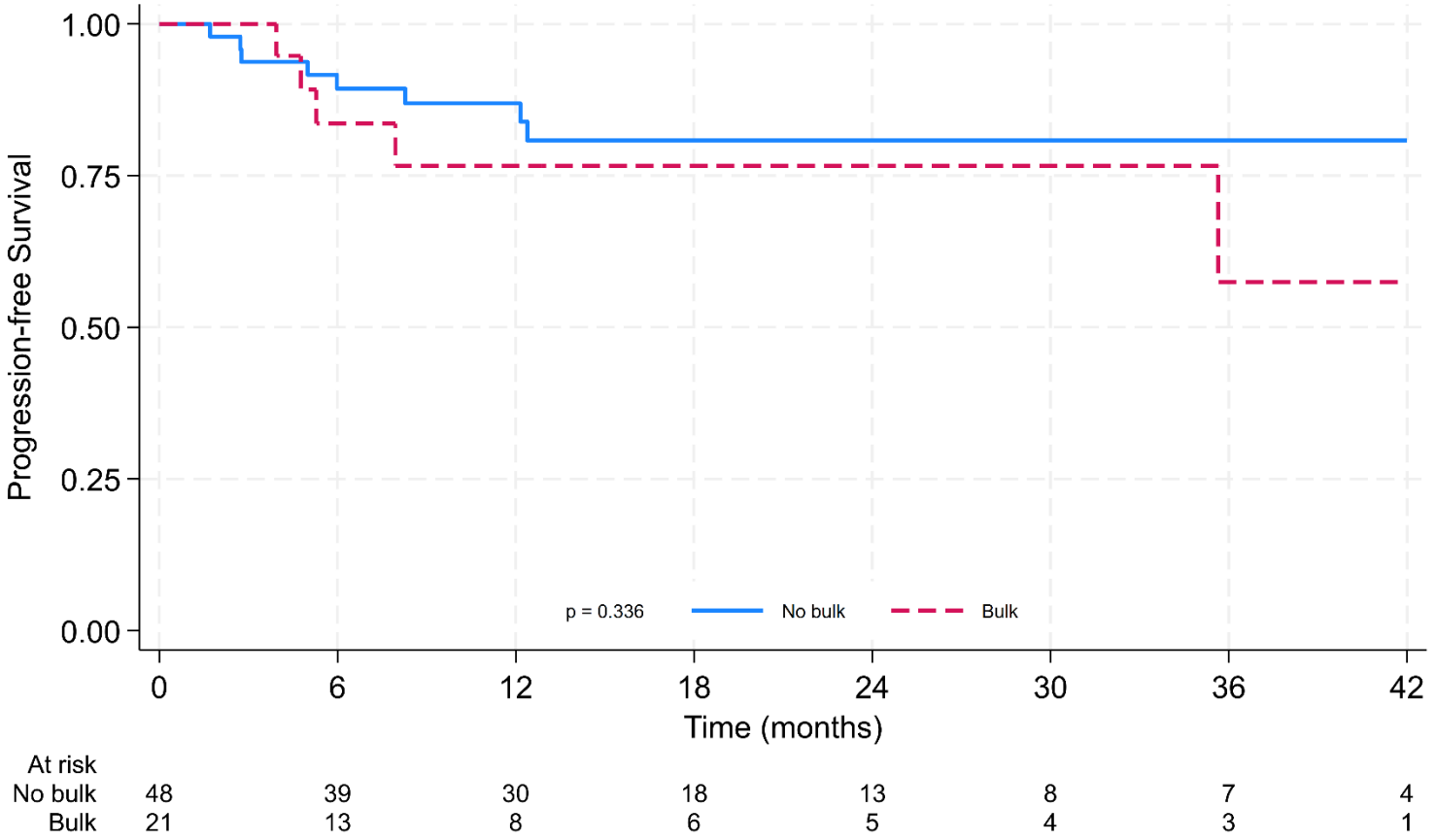
At risk								
No bulk	211	122	83	63	46	33	28	21
Bulk	44	27	19	18	11	10	9	6

(B)



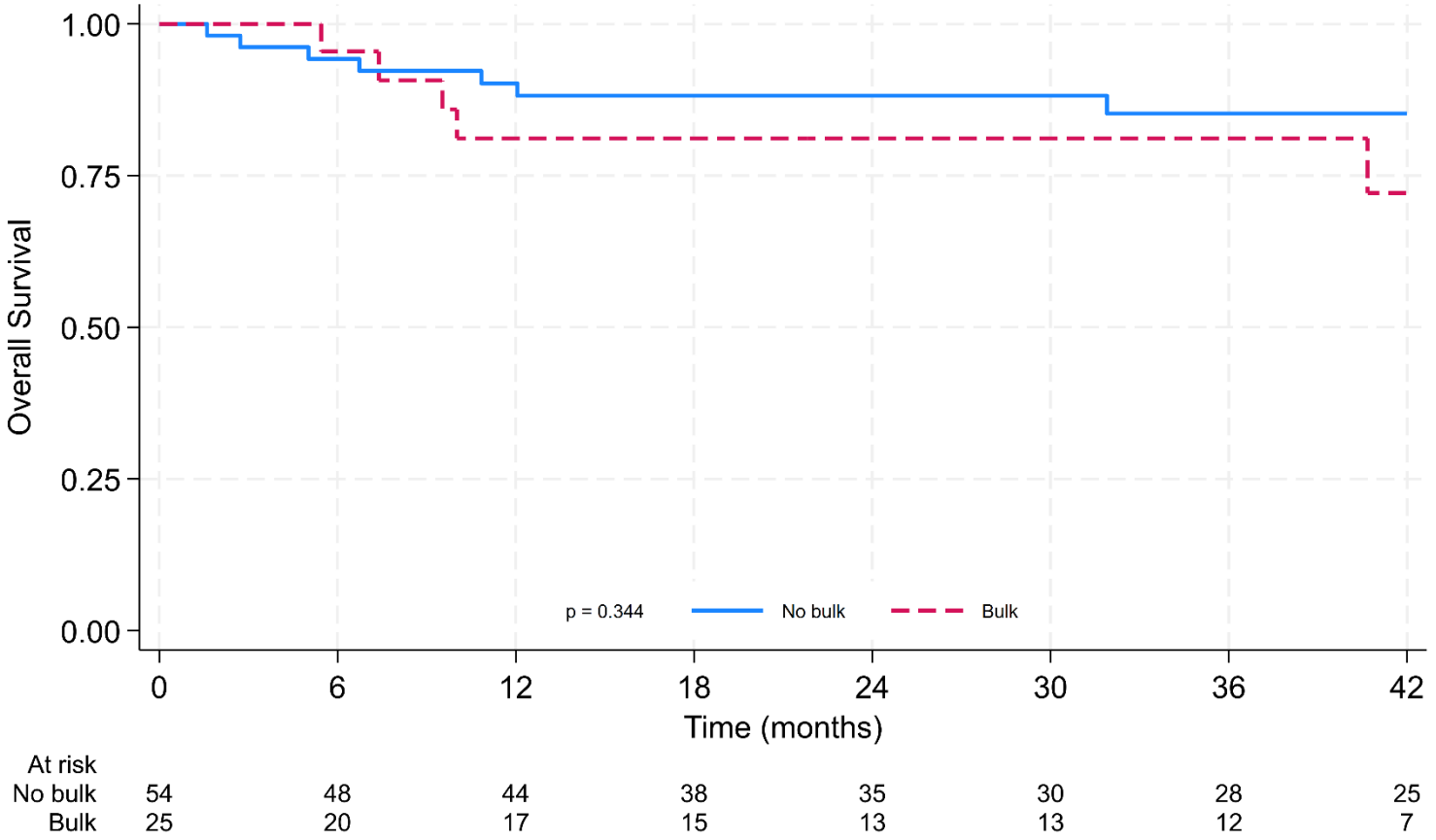
At risk								
No bulk	269	213	168	146	123	104	93	74
Bulk	49	41	35	30	26	20	18	16

(C)



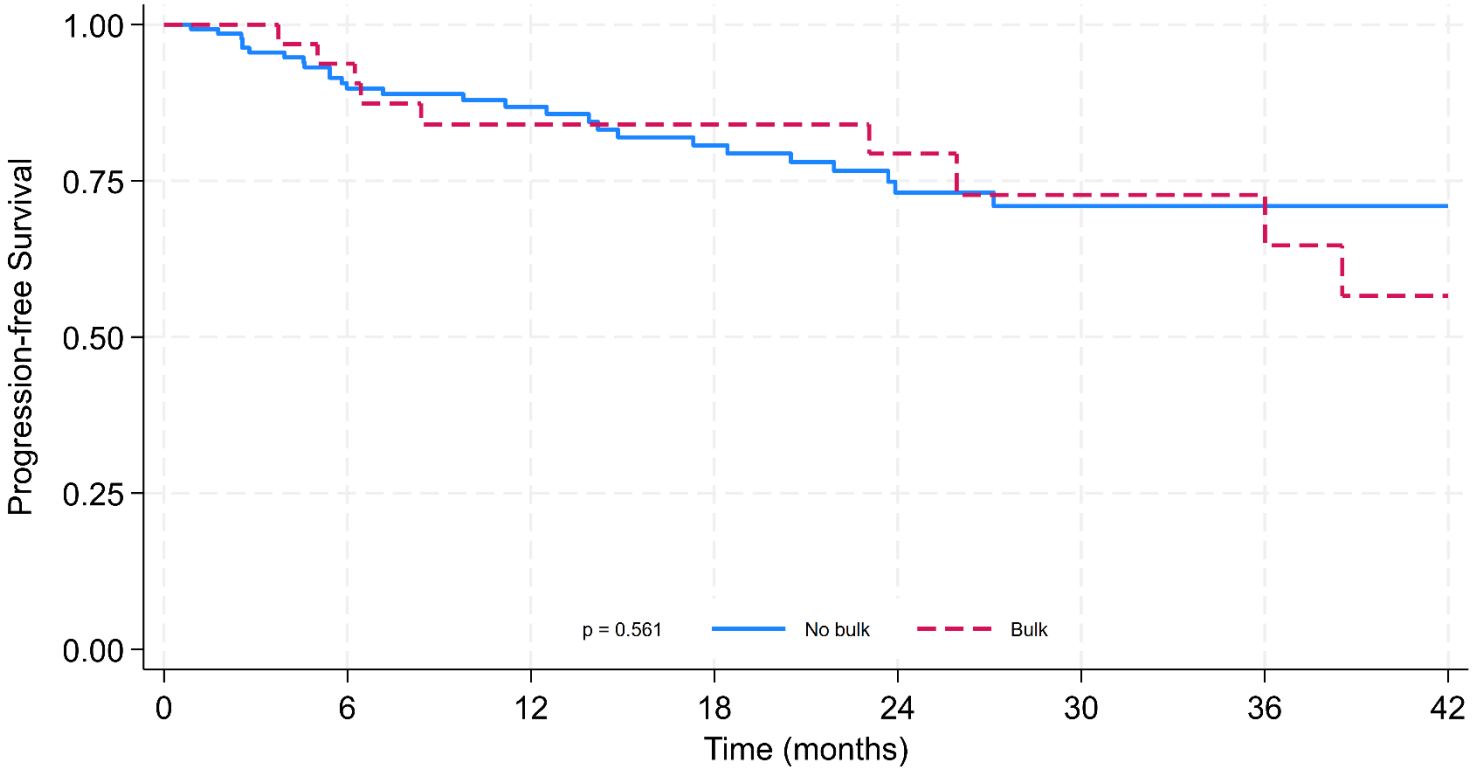
At risk								
No bulk	48	39	30	18	13	8	7	4
Bulk	21	13	8	6	5	4	3	1

(D)



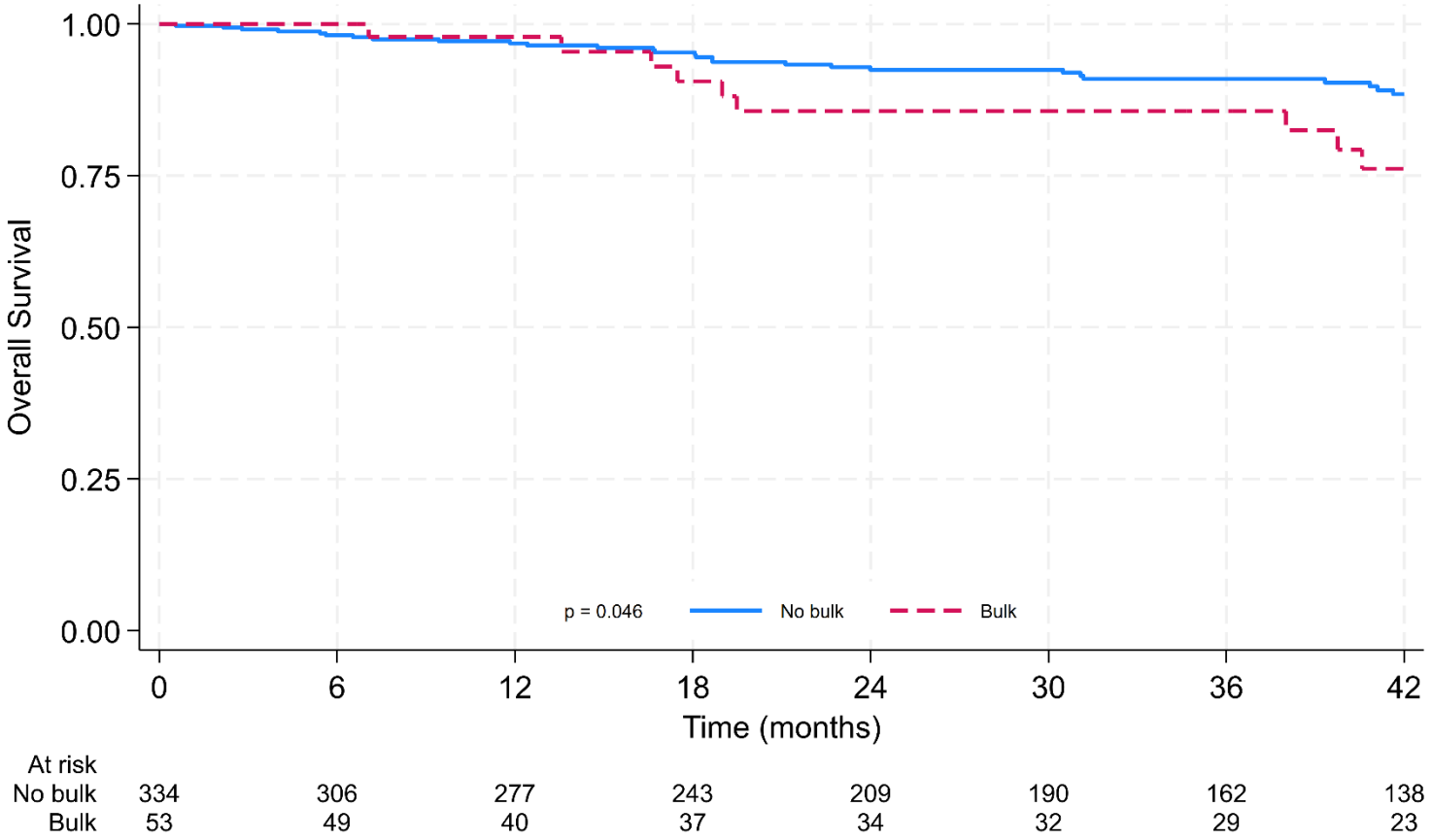
At risk								
No bulk	54	48	44	38	35	30	28	25
Bulk	25	20	17	15	13	13	12	7

(E)



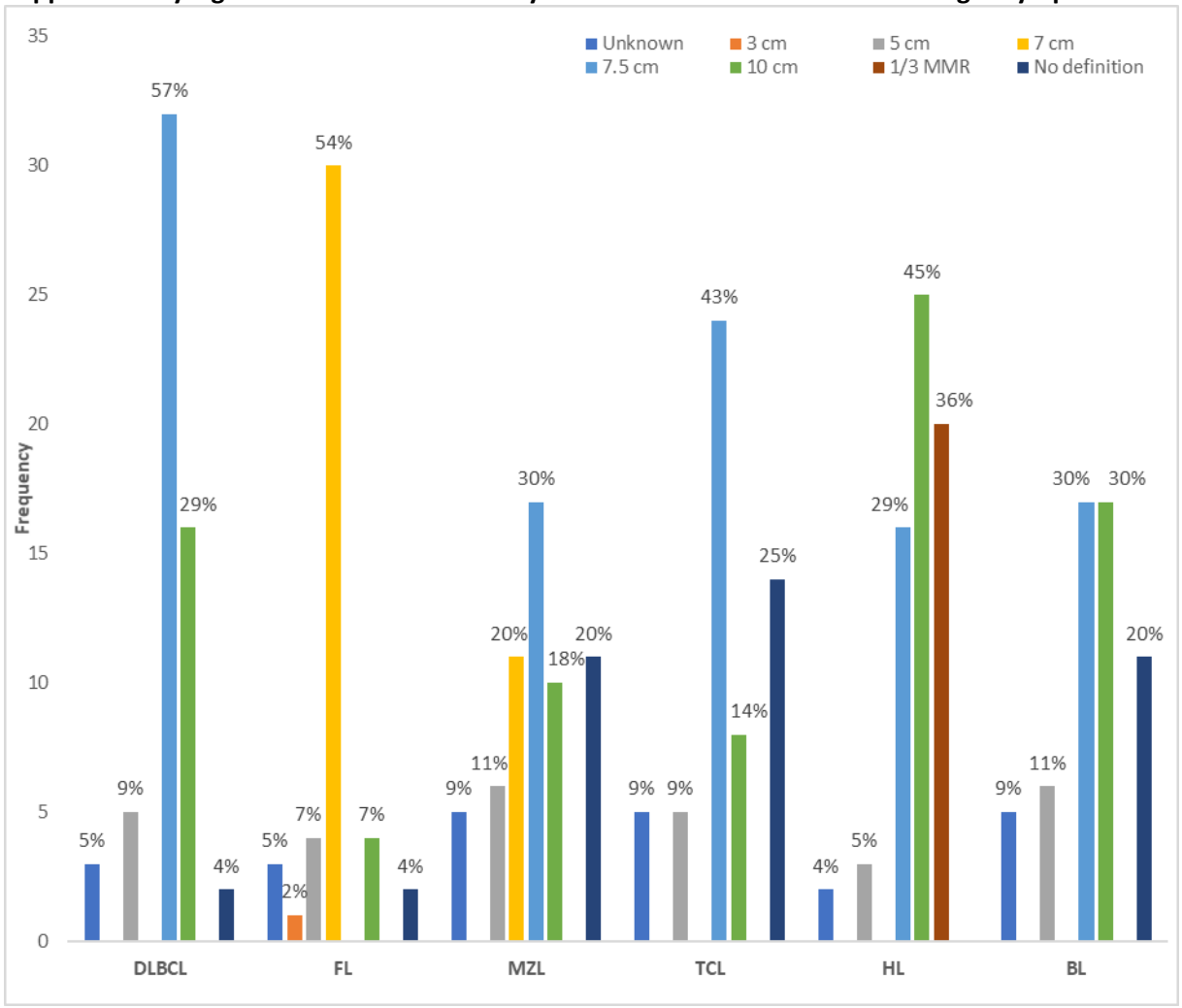
At risk								
No bulk	140	106	78	62	42	28	22	20
Bulk	32	30	23	21	14	11	9	7

(F)



At risk								
No bulk	334	306	277	243	209	190	162	138
Bulk	53	49	40	37	34	32	29	23

Supplementary Figure S2. Definitions used by LaRDR affiliated clinicians according to lymphoma subtype. MMR: mediastinal mass ratio.



Appendix: Participating sites and principal investigators at LaRDR

Dr Susan Morgan, Alfred Hospital; Dr Leanne Berkahn, Auckland City Hospital; Dr Tamara Marconi, Box Hill Hospital; A/Prof Melita Kenealy, Cabrini Health; Dr Emma-Jane McDonald, Christchurch Hospital; Dr Kyle Crassini, Coffs Harbour Health Campus; Prof Judith Trotman, Concord Hospital; Prof Miles Prince, Epworth Hospital; Dr Kate Manos, Flinders Medical Centre; A/Prof Tara Cochrane, Gold Coast University Hospital; Dr Tasman Armytage, Gosford Hospital; A/Prof Geoffrey Chong, Grampians Health; Dr Nicholas Viiala, Liverpool Hospital; Dr Rory Bennett, North Shore Hospital; Dr Teresa Leung, Northern Health; Prof Michael Dickinson, Peter MacCallum Cancer Centre; Dr Jock Simpson, Port Macquarie Base Hospital; Dr Annmarie Bosco, Prince of Wales Hospital; A/Prof Colm Keane, Princess Alexandra Hospital; Dr Hun Chuah, Rockingham General Hospital; Dr Pratyush Giri, Royal Adelaide Hospital; Dr May Chiu, Royal Darwin Hospital; Dr Luke Coyle, Royal North Shore Hospital; Dr John Balendra, Royal Perth Hospital; Prof Chan Cheah, Sir Charles Gairdner Hospital; A/Prof Matthew Ku, St Vincent's Hospital Melbourne; Prof Nada Hamad, St Vincent's Hospital Sydney; Dr Manjunath Narayana, Sunshine Coast University Hospital; Prof Dipti Talaulikar, The Canberra Hospital; Dr Howard Mutsando, Toowoomba Hospital; Dr Joel Wight, Townsville Hospital; Dr Sumita Ratnasingam, University Hospital Geelong; Dr Hayden Jina, Wellington Regional Hospital; Dr Ming Ong, Western Health.