

## Outcomes of Burkitt lymphoma with central nervous system involvement: evidence from a large multicenter cohort study

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**Supplemental Table S1.**

Univariate and multivariate logistic models for the association between clinical characteristics and baseline CNS involvement. Non-collinear variables with statistical significance in univariate models were included in the multivariable model.

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age >40	1.29	(0.85-1.97)	0.24			
Age >60	1.04	(0.65-1.66)	0.86			
Female sex	1.23	(0.78-1.92)	0.37			
HIV positive	2.34	(1.52-3.60)	0.001	1.84	(1.12-3.03)	0.017
B symptoms	1.61	(1.08-2.42)	0.020	0.99	(0.62-1.58)	0.96
ECOG 2-4	2.91	(1.86-4.55)	<0.001	2.13	(1.27-3.57)	0.004
Hemoglobin <11.5 g/dL	2.31	(1.52-3.50)	<0.001			
Albumin <3.5 g/dL	2.24	(1.47-3.42)	<0.001			
LDH > ULN	3.45	(1.73-6.89)	<0.001			
LDH >3x ULN *	2.53	(1.67-3.84)	<0.001	1.27	(0.76-2.11)	0.37
LDH >5x ULN	3.08	(2.02-4.68)	<0.001			
≥2 extranodal sites	3.47	(2.27-5.28)	<0.001	2.94	(1.75-4.94)	<0.001
Extranodal involvement:						
Bone marrow	5.07	(3.21-8.00)	<0.001	2.80	(1.59-4.94)	<0.001
Intestine	0.33	(0.16-0.67)	0.002	0.34	(0.16-0.72)	0.005
Liver	1.79	(1.06-3.00)	0.028	0.60	(0.32-1.11)	0.11
Pancreas	0.53	(0.16-1.79)	0.31			
Pleura/peritoneum	0.65	(0.34-1.24)	0.19			
Kidney/adrenal glands	2.61	(1.44-4.75)	0.002	1.21	(0.59-2.45)	0.61
Testis (men only)	2.35	(0.69-7.99)	0.17			
Uterus/ovary (women only)	2.26	(0.70-7.28)	0.17			
Female breast	1.56	(0.46-5.33)	0.48			

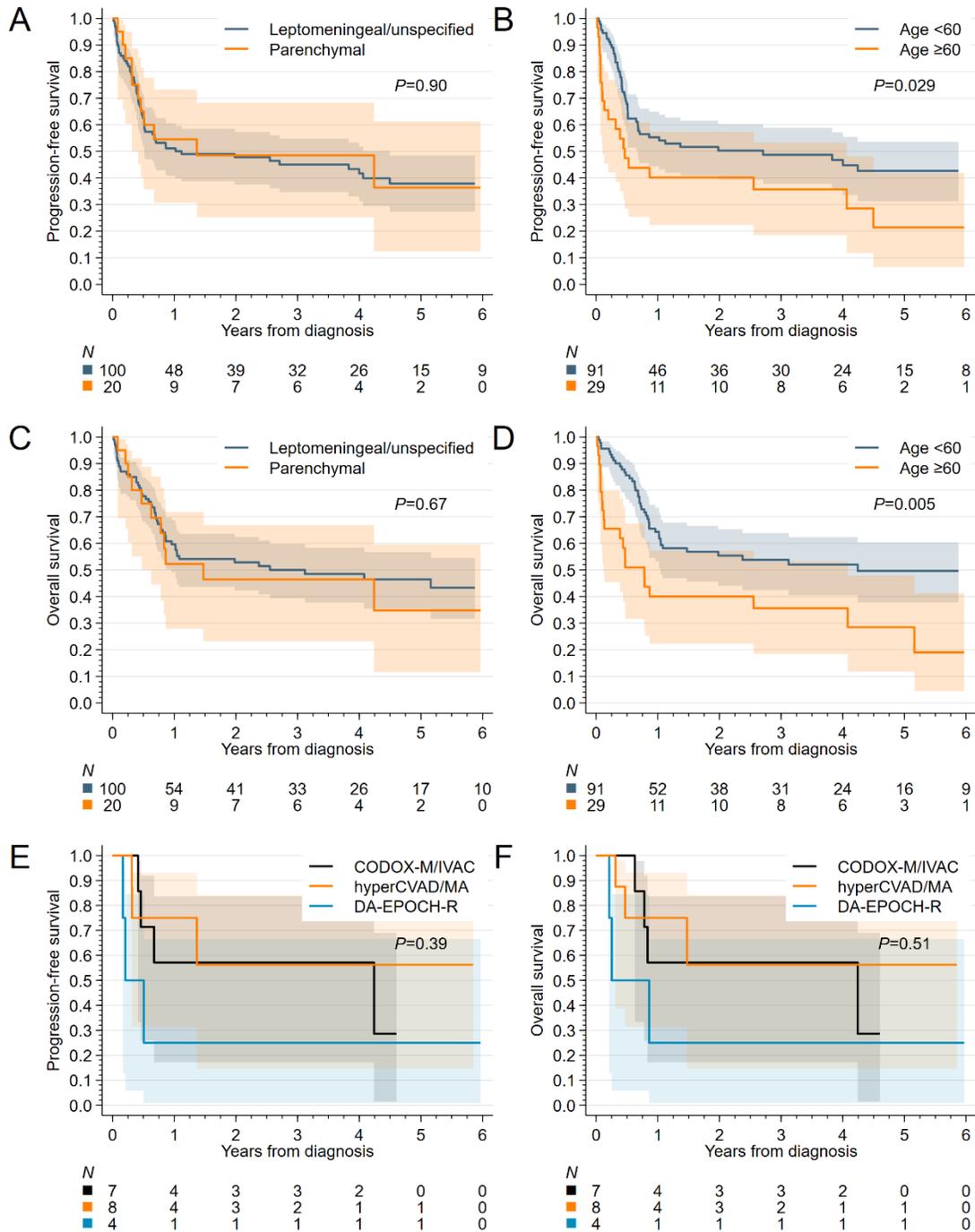
\* All LDH cutoffs, as well as hemoglobin and albumin, were studied, without a significant difference in results. LDH, hemoglobin, and albumin were collinear, so only LDH was included.

CI: confidence interval; CNS: central nervous system; ECOG : Eastern Cooperative Oncology Group performance status; LDH : lactate dehydrogenase; N/A: not applicable; OR: odds ratio; ULN: upper limit of normal

**Supplemental Fig. S1.**

**Factors associated with progression-free survival (PFS) and overall survival (OS) among patients with baseline CNS involvement:**

**(A)** PFS according to type of CNS involvement (parenchymal or leptomeningeal / unspecified); **(B)** PFS according to age at diagnosis; **(C)** OS according to type of CNS involvement (parenchymal or leptomeningeal / unspecified); **(D)** OS according to age at diagnosis; **(E)** PFS of patients with parenchymal CNS invasion, according to first-line regimen; **(F)** OS of patients with parenchymal CNS invasion, according to first-line regimen.

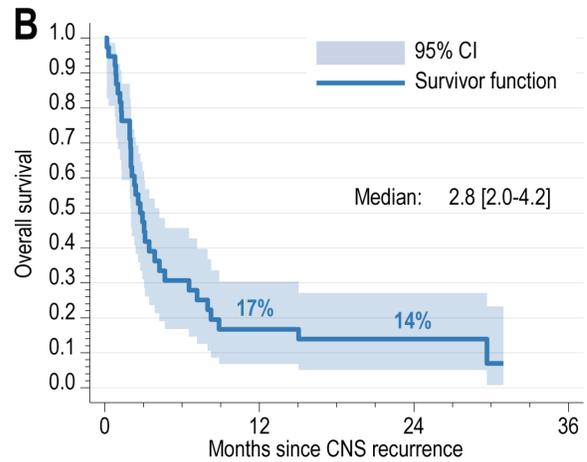
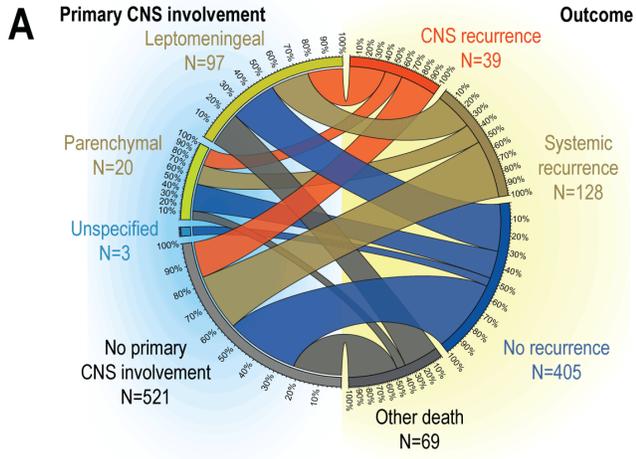


**Supplemental Fig. S2.**

**Outcomes of patients with CNS involvement:**

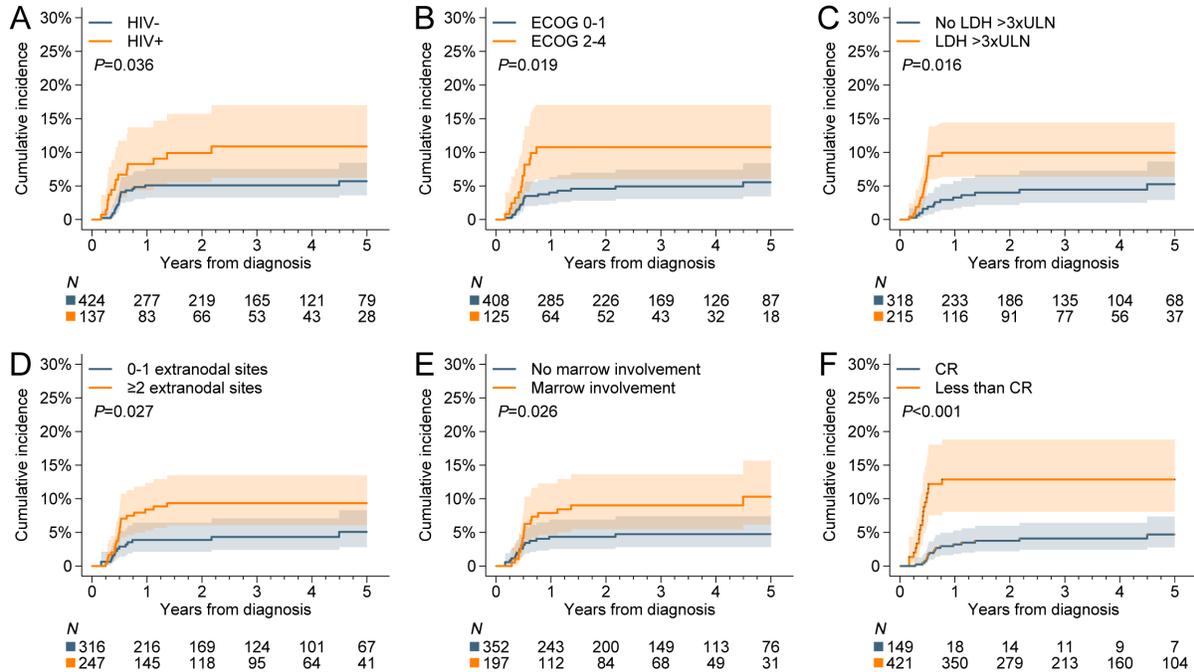
(A) Circos plot illustrating association between baseline CNS involvement and subsequent BL recurrence; note that patients with baseline involvement of both parenchymal and leptomeningeal compartments were included in the “parenchymal” category;

(B) overall survival after diagnosis of CNS recurrence; estimates at 12 and 24 months are given.



**Supplemental Fig. S3.**

**Factors associated with CNS recurrence:** (A) HIV status, (B) performance status, (C) LDH elevation, (D) involvement of  $\geq 2$  extranodal sites, (E) bone marrow involvement, and (F) achievement of complete response (CR) to first-line chemotherapy, among patients with BL ( $N=570$ ) treated with one of the standard NCCN-recommended regimens (CODOX-M/IVAC, hyperCVAD/MA, or DA-EPOCH-R);  $P$ -values are derived from univariate competing risk models.



**Supplemental Table S2.**

Patient characteristics stratified by receipt of high-intensity chemotherapy (CODOX-M/IVAC or hyperCVAD/MA) or DA-EPOCH-R.

	CODOX-M/IVAC or hyper-CVAD/MA		DA-EPOCH-R		P
	N	%	N	%	
N	389	(100)	181	(100)	
Age					<0.001
≤40	163	(42)	49	(27)	
41 to 60	168	(43)	67	(37)	
>60	58	(15)	65	(36)	
Sex					0.064
Male	286	(74)	146	(81)	
Female	103	(26)	35	(19)	
HIV infection	78	(20)	59	(33)	0.001
Stage 4	282	(73)	131	(72)	0.79
B symptoms	186	(48)	83	(46)	0.53
ECOG 2-4	71	(18)	54	(30)	0.002
Hemoglobin <11.5 g/dL	113	(29)	62	(34)	0.20
Albumin <3.5 g/dL	134	(34)	87	(48)	<0.001
LDH					
> ULN	280	(72)	131	(72)	0.72
>3x ULN	151	(39)	64	(35)	0.31
>5x ULN	108	(28)	41	(23)	0.14
≥2 extranodal sites	162	(42)	85	(47)	0.27
Extranodal involvement:					
CNS	74	(19)	35	(19)	0.93
Marrow	136	(35)	61	(34)	0.73
Intestine	60	(15)	41	(23)	0.035
Liver	51	(13)	27	(15)	0.56
Pancreas	15	(4)	9	(5)	0.54
Pleura/Peritoneum	56	(14)	24	(13)	0.72
Kidney/adrenal	34	(9)	15	(8)	0.86
Testis <sup>a</sup>	10	(4)	2	(1)	0.20
Uterus/ovary <sup>a</sup>	12	(12)	0	(0)	0.035
Female breast <sup>a</sup>	9	(9)	4	(11)	0.64

<sup>a</sup> Percentages and P values calculated for men or women only, as pertinent.

CNS: central nervous system; ECOG : Eastern Cooperative Oncology Group performance status; LDH : lactate dehydrogenase; N/A: not applicable; ULN: upper limit of normal

**Supplemental Fig. S4.**

**Cumulative incidence of CNS recurrence according to first-line chemotherapy regimen: (A) patients age  $\leq 60$ ; (B) patients age  $>60$ ; (C) patients with performance status ECOG 0-1; (D) patients with performance status ECOG 2-4; (E) patients without HIV infection; (F) patients with HIV infection; subhazard ratios (SHR) were derived from univariate competing risk models comparing hyperCVAD versus CODOX-M/IVAC, or DA-EPOCH-R versus both high-intensity regimens combined.**

