Outcome of HIV-associated non-Hodgkin lymphomas can be predicted by lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio

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BACKGROUND

Lymphomas have become the most common AIDS-related cancer in the developed world, constituting over 50% of all AIDS defining cancers and the most common cause of cancer-related death in HIV infected individuals

Lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are simple and effective biomarkers for both host immune homeostasis (e.g., ALC, tumor-infiltrating lymphocytes) and the tumor microenvironment (e.g., AMC, tumor-associate macrophages) that may predict clinical outcomes in non-Hodgkin lymphomas.

However, the association between these hematologic parameters and prognosis of HIV-associated lymphomas (HIV-L) has not been evaluated.

METHODS

Observational retrospective multi-cohort study.

All HIV-infected patients (pts) with a diagnosis of non-Hodgkin Lymphoma (NHL) between Jan 1, 2000 and Dec 31, 2013 in the ICONA cohort or in four collaborating hospital databases were included.

Patients were eligible if they had available absolute lymphocyte count, absolute monocyte count, and absolute platelet count at diagnosis of HIV-L. We chose the cut-off of 2.11 for LMR, 150 and 300 for PLT, and 4.35 for NLR, as reported in general population.

Characteristics at diagnosis were compared according to parameters strata. Overall survival (OS) estimates by KM and predictors of OS by multivariable Cox regression after adjusting for main potential confounders (calendar year, age, gender, HCV-coinfection status, IPI score, rituximab use CD4+ T cell count and ART use) were performed.

RESULTS

Two hundreds and sixty-one HIV-NHL pts were included (84% male, median age 46 years, median CD4+ cell count at diagnosis 210 cells/mm3). All pts were considered for PLR analysis, while 191 for NLR and 177 for LMR.

Low LMR at diagnosis (<2.11) was significantly associated with HCV-coinfection, poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) and low CD4+ T cell count (table 1).

Pts with PLR<150 exhibited significantly higher prevalence of HBV coinfection, poor ECOG PS and low CD4+ T cell count(table 2), while pts with high NLR (>4.35) showed significant lower prevalence of HCV coinfection (table 3).

After a median follow-up of 28 months (IQR 9-72), 104 (39.8%) NHl patients died.

By 3-years from diagnosis, the cumulative risk of death was 62% (95%CI 48, 77) versus 27% (95%CI 19, 36) for LMR<2.11 and >2.11; 48% (95%CI 31, 64) versus 33% (95%CI 25, 40) for NLR>4.35 and <4.35; 55% (95%CI 43, 66) versus 34% (95%CI 25, 42) versus 35% (95%CI 22, 49) for PLR <150, 150-300, >300 (Figure1-3).

At multivariable analysis, LMR and PLR were independently associated with increased risk of death after a diagnosis of NHL (table 4).

CONCLUSIONS

Our analysis shows that decreased LMR and PLR are associated with poor prognosis in HIV+ patients with NHL and show an adverse effect on NHL-HIV+ patients.

LMR and PLR at diagnosis are simple tool that assess the host's immune homeostasis and the tumor microenvironment.

A decreased LMR and PLR represent a decreased lymphocyte count and/or an increased monocyte or platelet count. Therefore, LMR and PLR can reflect the status of pro-tumor and antitumor ability in response to inflammation.

The evidence by our study that LMR and PLR could be applied also to HIV-infected population affected by NHL supports its use in stratification of patients and determination of specific therapeutic plans.

Table 1 – Characteristics of pts according to LMR group

	LMR groups			
	>2.11 N= 117	0-2.11 N=60	Total N=177	p
Age, years	47 (43-52)	46 (39-51)	47 (42-52)	0.086
Gender, female	16 (13.7%)	11 (18.3%)	27 (15.3%)	0416
Epidemiology				
IDU	20 (22.0%)	11 (18.3%)	29 (21.0%)	0.084
MSM	26 (28.6%)	9 (19.1%)	35 (25.4%)	
Heterosexual	23 (25.3%)	9 (19.1%)	42 (30.4%)	
Other	22 (24.2%)	19 (40.4%)	32 (23.2%)	
HbsAg+	5 (5.0%)	10 (21.3%)	13 (8.3%)	0.704
HCVAb+	38 (33.9%)	8 (14.5%)	56 (32.9%)	0.039
Year lymphoma diagnosis	2010 (2006-2012)	2011 (2008-2012)	2010 (2007-2012)	0.139
Histotype				
DLBCL	65 (57.0%)	31 (54.4%)	96 (56.1%)	0.006
Immunoblastic	11 (9.6%)	4 (7.0%)	15 (8.8%)	
Burkitt	38 (33.3%)	16 (28.1%)	54 (31.6%)	
Plasmablastic	0 (0.0%)	6 (10.5%)	6 (3.5%)	
Start ART	109 (93.2%)	53 (88.3%)	162 (91.5%)	0.276
IPI				
Low	22 (18.8%)	15 (25.0%)	37 (20.9%)	0.596
Medium	54 (46.2%)	24 (40.0%)	78 (44.1%)	
High	11 (9.4%)	8 (13.3%)	19 (10.7%)	
Stage B	47 (44.3%)	31 (57.4%)	78 (48.8%)	0.119
ECOG scale 3-4	18 (21.4%)	19 (41.3%)	37 (28.5%)	0.017
Extranodal site>2	38 (38.0%)	17 (32.1%)	55 (35.9%)	0.469
Stage				
1	78 (68.4%)	35 (62.5%)	113 (66.5%)	0.669
2	16 (14.0%)	12 (21.4%)	28 (16.5%)	
3	20 (17.5%)	9 (16.1%)	39 (17.1%)	
4	56 (49.1%)	26 (46.4%)	82 (48.2%)	
CD4 count, cells/mm3	260 (154, 469)	151 (76, 269)	218 (110, 411)	0.006
HIV-RNA log10 cp/ml	1.82 (1.58, 4.51)	4.35 (1.59, 5.16)	2.15 (1.59, 4.85)	0.118

Table 2 – Characteristics of pts according to NLR group

	NLR groups			
	0-4.35 N= 150	>4.35 N=41	Total N=191	p
Age, years	47 (42-52)	46 (38-51)	46 (40-52)	0.561
Gender, female	23 (15.3%)	7 (17.1%)	30 (15.7%)	0.787
Epidemiology				
IDU	28 (23%)	7 (17.1%)	33 (21.9%)	0.243
MSM	29 (23.8%)	5 (17.2%)	35 (23.1%)	
Heterosexual	40 (32.8%)	6 (20.7%)	50 (33.1%)	
Other	25 (20.5%)	25 (20.5%)	33 (21.9%)	
HbsAg+	6 (4.6%)	8 (27.6%)	13 (7.7%)	0.339
HCVAb+	45 (31.3%)	7 (18.4%)	60 (33.%)	0.005
Year lymphoma diagnosis	2010 (2006-2012)	2011 (2008-2013)	2010 (2006-2012)	
Histotype				
DLBCL	82 (56.2%)	24 (61.5%)	106 (57.3%)	0.750
Immunoblastic	12 (8.2%)	3 (7.7%)	15 (8.1%)	
Burkitt	48 (32.9%)	10 (25.6%)	58 (31.4%)	
Plasmablastic	4 (2.7%)	2 (5.1%)	6 (3.2%)	
Start ART	139 (92.7%)	36 (87.8%)	175 (91.6%)	0.321
IPI				
Low	28 (18.7%)	11 (26.8%)	39 (20.4%)	0.654
Medium	67 (44.7%)	18 (43.9%)	85 (44.5%)	
High	16 (10.7%)	4 (9.8%)	20 (10.5%)	
Stage B	68 (50.7%)	20 (52.6%)	88 (51.2%)	0.838
ECOG scale 3-4	31 (27.2%)	7 (23.3%)	38 (26.4%)	0.671
Extranodal site>2	46 (35.9%)	11 (31.4%)	57 (35.0%)	0.621
Stage				
1	95 (66.0%)	25 (64.1%)	120 (65.6%)	0.743
2	23 (16.0%)	6 (15.4%)	29 (15.8%)	
3	26 (18.1%)	8 (20.5%)	34 (18.6%)	
4	71 (49.3%)	16 (41.0%)	87 (47.5%)	
CD4 count, cells/mm3	233 (123, 493)	174 (88, 88)	218 (111, 111)	0.081
HIV-RNA log10 cp/ml	2.15 (1.59, 4.68)	3.69 (1.57, 5.26)	2.37 (1.59, 1.59)	0.424

Table 3 – Characteristics of pts according to PLR group

	PLR groups			
	>300 N= 53	150-300 N=122	0-150 N=86	p
Age, years	47 (38-52)	46 (39-51)	47 (41-52)	0.559
Gender, female	11 (20.8%)	24 (19.7%)	11 (12.8%)	0.352
Epidemiology				
IDU	5 (12.8%)	24 (19.7%)	24 (32.4%)	0.142
MSM	12 (30.8%)	22 (21.6%)	14 (18.9%)	
Heterosexual	11 (28.2%)	26 (25.5%)	20 (27.0%)	
Other	11 (28.2%)	29 (28.4%)	16 (21.6%)	
HbsAg+	1 (2.5%)	25 (24.5%)	10 (14.7%)	0.009
HCVAb+	9 (20.0%)	8 (8.9%)	35 (45.5%)	0.111
Year lymphoma diagnosis	2009 (2006-2012)	2009 (2004-2012)	2009 (2006-2012)	0.222
Histotype				
DLBCL	29 (56.9%)	74 (61.7%)	52 (62.7%)	0.340
Immunoblastic	2 (3.9%)	13 (10.8%)	4 (4.8%)	
Burkitt	18 (35.3%)	32 (26.7%)	24 (28.9%)	
Plasmablastic	2 (3.9%)	1 (0.8%)	3 (3.6%)	
Start ART	48 (90.6%)	113 (92.6%)	77 (89.5%)	0.730
IPI				
Low	10 (18.9%)	21 (17.7%)	9 (10.5%)	0.781
Medium	20 (37.7%)	42 (34.4%)	34 (39.5%)	
High	5 (9.4%)	9 (7.4%)	8 (9.3%)	
Stage B	21 (46.7%)	47 (48.0%)	45 (60.8%)	0.179
ECOG scale 3-4	10 (30.3%)	13 (18.8%)	20 (39.2%)	0.346
Extranodal site>2	19 (42.2%)	30 (30.3%)	21 (31.3%)	0.061
Stage				
1	40 (76.9%)	81 (69.2%)	57 (69.5%)	0.567
2	8 (15.4%)	17 (14,5%)	9 (11.0%)	
3	4 (7.7%)	19 (16.2%)	16 (19.5%)	
4	33 (63.5%)	62 (53.0%)	47 (57.3%)	
CD4 count, cells/mm3	232 (173, 510)	168 (78, 383)	183 (73, 322)	0.047
HIV-RNA log10 cp/ml	2.94 (1.69,5.13)	2.96 (1.69, 4.77)	3.62 (1.69, 5.02)	0.848

Table 4 – Relative hazard of death from fitting a Cox regression model

	NHL *		
Hematologic parameter&	RH	95%CI	p-value
NLR			
>4.35 vs. <4.35	2.34	0.87-6.33	0.09
LMR			
<2.11 vs. >2.11	3.11	1.20-8.09	0.02
PLR			
Per level lower#	2.26	1.17-4.39	0.01

*Adjusted for age, gender, calendar year of lymphoma diagnosis, use of rituximab, age-adjusted IPI score , CD4+ and HIV-RNA at lymphoma diagnosis

levels: 0-150 low; 150-300 intermediate; >300 high

&Three separate models with one hematological parameter included at the time

Figure 1 – Risk of death according to LMR strata

B)

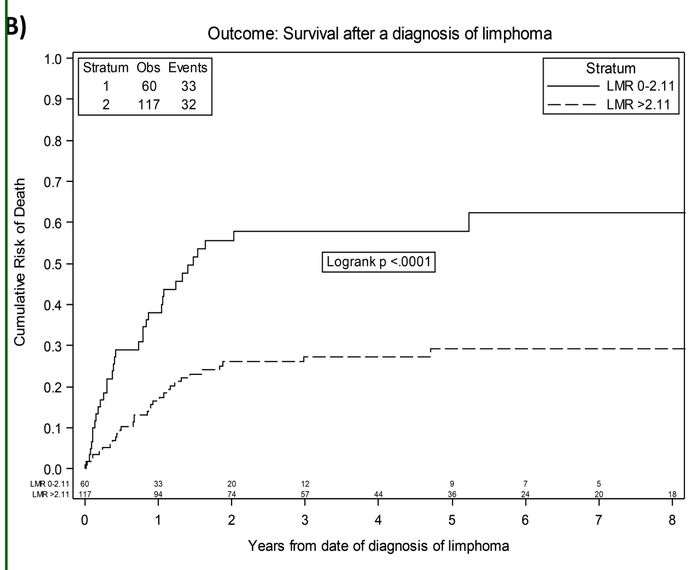


Figure 2 – Risk of death according to NLR strata

A)

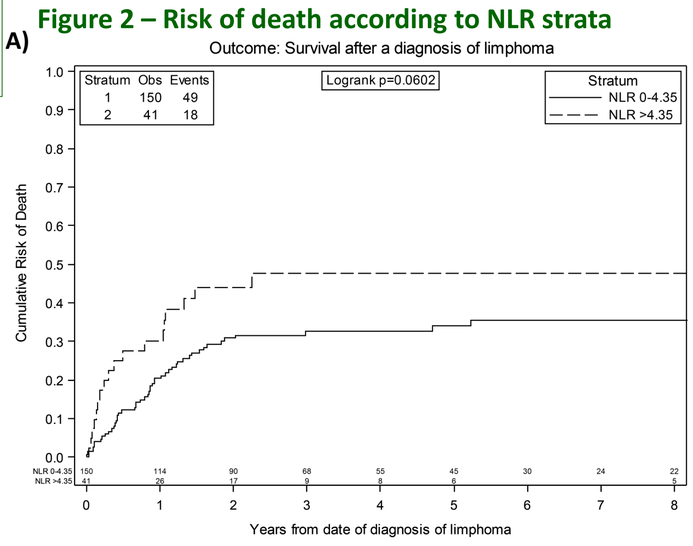
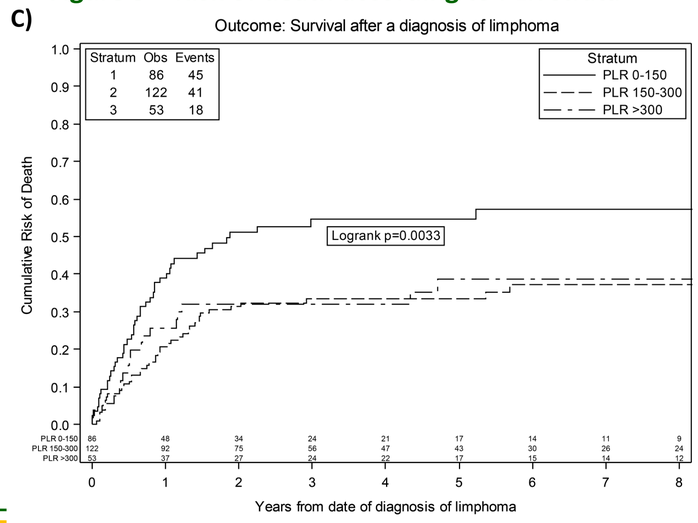


Figure 3 – Risk of death according to PLR strata

C)



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