

Lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio predict survival in HIV-infected patients with non-Hodgkin lymphomas

A. Bandera^{1*}, A. Cozzi Lepri², L. Galli³, N. Galizzi³, G.M. Baldin⁴, L. Teofili⁴, V. Mazzotta⁵, L. Alba⁵, A. Castagna³, A. Gori¹, A. d'Arminio Monforte⁶, A. Antinori⁵, A. Cingolani⁴ for the Icona Foundation Study Group.

¹ San Gerardo Hospital, Monza, Italy; ² University College London, London, UK; ³ HSR, San Raffaele Hospital, Milano, Italy; ⁴ Catholic University, Roma, Italy; ⁵ National Institute for Infectious Diseases, L. Spallanzani, Roma, Italy; ⁶ San Paolo Hospital, University of Milano, Milano, Italy

Background

- Lymphoma is a leading cause of death among HIV-infected individuals with cancer
- Studies have reported on the role of lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) to predict the prognosis of various types of malignant lymphoma.
- However, the association between these hematologic markers and prognosis of HIV-associated lymphomas (HIV-L) has not been evaluated.

Study Design and Methods

- Retrospective analysis of the data collected in an observational multi-cohort study.
- All HIV-infected patients (pts) with a diagnosis of HIV-L (non-Hodgkin Lymphoma, NHL; Hodgkin disease, HD) between Jan 1, 2000 and Dec 31, 2013 in the ICONA cohort or in four collaborating hospital databases were included.
- Pts were eligible if they had ≥ 1 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, to define abnormal values as reported in general population.
- Characteristics at time of cancer diagnosis were compared using chi-square and non-parametric tests for the median as appropriate. 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 for NHL, AVBD use and stage of disease for HD, CD4+ T cell count and ART use) were performed.

Results

- Three hundreds and eighty-five HIV-L pts were included (261 NHL and 124 HD, 85% male, median age 45 years, median CD4+ cell count at diagnosis 232 cells/mm³).
- In NHL, low LMR at diagnosis (< 2.11) was significantly associated with HCV-coinfection (0.039) and poor Eastern Cooperative Oncology Group Performance Status (ECOG PS, $p=0.01$), pts with high NLR (> 4.35) showed significant lower prevalence of HCV coinfection ($p=0.005$), while pts with PLR < 150 exhibited significantly higher prevalence of HBV coinfection ($p=0.009$) and poor ECOG PS ($p=0.048$) (table 1,2,3).
- In HD patients, low LMR (< 2.11) was associated with higher prevalence of B symptoms ($p=0.016$), high NLR group (> 4.35) had more frequently multiple extra-nodal sites (> 2) ($p=0.019$), while low PLR (< 150) were not significantly associated with any of the considered clinical factors.
- After a median follow-up of 28 months (IQR 9-72), 104 (39.8%) NHL patients and 35 (28.2%) HD patients died.
- By 3-years from diagnosis, the cumulative risk of death for NHL was 62% (95%CI 48, 77) for LMR < 2.11 versus 27% (95%CI 19, 36) for LMR > 2.11 ; 48% (95%CI 31, 64) for NLR > 4.35 versus 33% (95%CI 25, 40) for < 4.35 ; 55% (95%CI 43, 66) for PLR < 150 , 34% (95%CI 25, 42) in 150-300 groups, versus 35% (95%CI 22, 49), > 300 (table 4, figure 1).

Table 1. Characteristics of NHL patients at cancer diagnosis according to LMR groups

	LMR groups			p
	> 2.11 N=117	0-2.11 N=60	Total N=177	
Age, years	47 (43-52)	46 (39-51)	47 (42-52)	0.086
Gender, female	16 (13.7%)	11 (18.3%)	27 (15.3%)	0.416
Epidemiology				0.084
IDU	20 (22.0%)	11 (18.3%)	29 (21.0%)	
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				0.006
DLBCL	65 (57.0%)	31 (54.4%)	96 (56.1%)	
Immunoblastic	11 (9.6%)	4 (7.0%)	15 (8.3%)	
Burkitt	38 (33.3%)	16 (28.1%)	54 (31.3%)	
Plasmablastic	0 (0.0%)	6 (10.5%)	6 (3.5%)	
Start ART	109 (93.2%)	53 (88.3%)	162 (91.5%)	0.276
IPI				0.596
Low	22 (18.8%)	15 (25.0%)	37 (20.9%)	
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				0.669
1	78 (68.4%)	35 (62.5%)	113 (66.5%)	
2	16 (14.0%)	12 (21.4%)	28 (16.5%)	
3	20 (17.5%)	9 (16.1%)	33 (17.1%)	
4	56 (49.1%)	26 (46.4%)	82 (48.2%)	

Table 3. Characteristics of NHL patients at cancer diagnosis according to PLR groups

	PLR groups			p
	> 300 N=53	150-300 N=122	0-150 N=66	
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				0.142
IDU	5 (12.8%)	24 (19.7%)	24 (32.4%)	
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				0.340
DLBCL	29 (56.9%)	74 (61.7%)	52 (62.7%)	
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				0.781
Low	10 (18.9%)	21 (17.7%)	9 (10.5%)	
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%)	0.048
Extranodal site > 2	19 (42.2%)	30 (30.3%)	21 (31.3%)	0.061
Stage				0.567
1	40 (76.9%)	81 (69.2%)	57 (69.5%)	
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%)	

Conclusions

- Our analysis shows that, in HIV-infected people with NHL, routinely collected markers such as LMR and PLR are associated with OS independently of established confounding factors and can be used to predict prognosis after diagnosis.
- This result suggests that decreased LMR and PLR might lead to a weak anti-tumor immunity and could be used as a negative prognostic biomarker in NHL.
- There was no evidence for an association between the markers and risk of mortality in patients with HD, although this might be due to low statistical power for NLR and PLR.

Table 2. Characteristics of NHL patients at cancer diagnosis according to NLR groups

	NLR groups			p
	0-4.35 N=150	> 4.35 N=41	Total N=191	
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				0.243
IDU	28 (23%)	7 (17.1%)	33 (21.9%)	
MSM	29 (23.8%)	5 (11.7%)	36 (23.1%)	
Heterosexual	40 (33.8%)	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 (33.3%)	0.005
Year lymphoma diagnosis	2010 (2006-2012)	2011 (2008-2013)	2010 (2006-2012)	
Histotype				0.750
DLBCL	82 (56.2%)	24 (61.5%)	106 (57.3%)	
Immunoblastic	12 (8.2%)	3 (7.7%)	15 (8.1%)	
Burkitt	45 (32.8%)	10 (25.8%)	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				0.654
Low	28 (18.7%)	11 (26.8%)	39 (20.4%)	
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				0.743
1	95 (66.0%)	25 (64.1%)	120 (65.6%)	
2	23 (16.0%)	6 (15.4%)	29 (16.8%)	
3	26 (18.1%)	8 (20.5%)	34 (18.6%)	
4	71 (49.3%)	16 (41.0%)	87 (47.5%)	

Table 4. Relative hazard of death from fitting a Cox regression model separately for NHL and HD

Hematologic parameter ^a	NHL			HD		
	aRH*	95%CI	p-value	aRH**	95%CI	p-value
NLR						
> 4.35 vs. < 4.35	2.14	0.76-6.00	0.15	4.19	0.49-35.90	0.19
LMR						
< 2.11 vs. > 2.11	3.66	1.34-10.01	0.01	1.13	0.68-1.89	0.63
PLR						
Per level lower ^b	3.08	1.37-6.90	0.006	0.65	0.15-2.69	0.54

aRH = adjusted Relative Hazard
*Adjusted for age, gender, calendar year of lymphoma diagnosis, use of rituximab, age-adjusted IPI score, CD4+, HIV-RNA and HCV co-infection status at lymphoma diagnosis
**Adjusted for age, gender, calendar year of lymphoma diagnosis, stage of disease, 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 in NHL patients according to: a) NLR strata; b) LMR strata; c) PLR strata.

