

Dettaglio abstract

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Title: Pre-ART platelet-to-lymphocyte ratio and the risk of serious non-AIDS-events, AIDS-events and mortality in PLWH starting first-line ART

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Mental health and predictors of AIDS and non-AIDS defining co-pathologies

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Abstract

Background: Among people living with HIV (PLWH) on effective antiretroviral therapy (ART), serious non-AIDS events (SNAEs) have become the major cause of morbidity and mortality and linked to systemic inflammation. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) were shown to be good indicators of inflammation and prognostic factors for different conditions in the general population but similar association analyses conducted in PLWH are sparse.

Methods: PLWH starting first line ART (baseline) between 1997-2021 enrolled in the ICONA Foundation Study cohort with a measure of the NL, PL and LM ratios over the 6 months before ART initiation were included. PLR, NLR and LMR values were divided in 3 subgroups based on the tertiles of the baseline distribution (T1, T2, T3). PLWH's characteristics at baseline were compared across the tertile groups using chi-square and Mann-Whitney test. The association between baseline PLR, NLR and LMR and the risk of SNAEs and death, AIDS events and all-cause mortality were tested using Kaplan-Meier and Cox proportional hazard models adjusting for a priori identified confounding factors (age, CD4 count, VL, HCV status and year of starting ART).

Results: We included 9,248 pts in the PLR analysis, 8,727 pts in the NLR analysis and 1,090 pts in the LMR analysis. Exact values of the tertiles for the considered ratios are shown in Tables/Figure. Participants were mainly males, 43% MSM, aged 38 years, with a median baseline CD4 count of 330/mm³. Baseline PLR was significantly associated with age, female gender, mode of HIV transmission, nationality, AIDS diagnosis, hepatitis coinfection (HBV and HCV), current and nadir CD4 count, CD8 count, smoking and lower time from HIV diagnosis (Table 1). After a median (IQR) follow-up of 5.0 (2.2-8.7) years, 489 SNAEs, 390 AIDS-events and 371 deaths were observed. By 15 years from starting ART, the risk of SNAE or death was 23% in PLWH with PLR<T1 vs. 18% in those with PLR=T2 vs 19% in those with PLR>T3 (Table 2, p=0.01). This difference was strongly significant and confirmed for SNAEs or death and all-cause mortality after the adjustment (Figure 1). Similarly, in the unadjusted analysis, there was a difference in risk of SNAE/death across tertiles of NLR and LMR (Table 2, log-rank p<0.0001 and p<0.0001, respectively). However, none of these associations retained statistical significance after controlling for age, CD4 count, VL, HCV status and year of starting ART. Results were similar for the other two endpoints.

Conclusions: Our data show that in PLWH starting a first-line ART, baseline PLR is a strong predictor of the risk of SNAEs, and mortality independently of key confounding factors. Because the biomarker is derived from common blood parameters routinely collected in the clinics, its use should be encouraged to identify and carefully manage PLWH who are at increased risk of poor long-term clinical outcomes.

Table 1. Characteristics of PLWHV according to PLR ratio tertile

Characteristics at starting cART	Tertile of PLR			p-value*	Total N= 9248
	T1 N= 3083	T2 N= 3085	T3 N= 3080		
Gender, n(%)				<.001	
Female	463 (15.0%)	681 (22.1%)	978 (31.8%)		2122 (22.9%)
Mode of HIV Transmission, n(%)				<.001	
PWID	597 (19.4%)	436 (14.1%)	387 (12.6%)		1420 (15.4%)
MSM	1388 (45.0%)	1390 (45.1%)	1039 (33.7%)		3817 (41.3%)
Heterosexual contacts	952 (30.9%)	1114 (36.1%)	1444 (46.9%)		3510 (38.0%)
Other/Unknown	146 (4.7%)	145 (4.7%)	210 (6.8%)		501 (5.4%)
Nationality, n(%)				0.001	
Not Italian	763 (24.7%)	934 (30.3%)	1150 (37.3%)		2847 (30.8%)
AIDS diagnosis, n(%)				<.001	
Yes	150 (4.9%)	165 (5.3%)	668 (21.7%)		983 (10.6%)
CVD diagnosis, n(%)				0.337	
Yes	23 (0.7%)	19 (0.6%)	29 (0.9%)		71 (0.8%)
HBeAg, n(%)				0.009	
Negative	2595 (84.2%)	2579 (83.6%)	2630 (85.4%)		7804 (84.4%)
Positive	28 (0.9%)	25 (0.8%)	8 (0.3%)		61 (0.7%)
Not tested	460 (14.9%)	481 (15.6%)	442 (14.4%)		1383 (15.0%)
HCVAb, n(%)				<.001	
Negative	2029 (65.8%)	2204 (71.4%)	2205 (71.6%)		6438 (69.6%)
Positive	642 (20.8%)	441 (14.3%)	400 (13.0%)		1483 (16.0%)
Not tested	412 (13.4%)	440 (14.3%)	475 (15.4%)		1327 (14.3%)
Hepatitis co-infection, n(%)				<.001	
No	1914 (62.1%)	2075 (67.3%)	2139 (69.4%)		6128 (66.3%)
Yes	660 (21.4%)	460 (14.9%)	405 (13.1%)		1525 (16.5%)
Not tested	509 (16.5%)	550 (17.8%)	536 (17.4%)		1595 (17.2%)
Calendar year of starting cART					
Median (IQR)	2012 (2003, 2016)	2013 (2005, 2016)	2013 (2006, 2017)		2013 (2004, 2016)
Age, years				<.001	
Median (IQR)	38 (31, 46)	37 (31, 45)	39 (33, 47)		38 (32, 46)
CD4 count, cells/mm³				<.001	
Median (IQR)	404 (276, 579)	370 (254, 505)	195 (54, 337)		330 (184, 479)
CD4 count nadir, cells/mm³				<.001	
Median (IQR)	383 (260, 536)	351 (240, 476)	186 (51, 321)		312 (174, 452)
CD8 count, cells/mm³				<.001	
Median (IQR)	1270 (920, 1706)	899 (703, 1153)	559 (376, 766)		866 (590, 1243)
CD4 count, n(%)				<.001	
<= 200 cells/mm ³	436 (14.2%)	530 (17.2%)	1552 (51.1%)		2518 (27.4%)
Time from HIV diagnosis, months				<.001	
Median (IQR)	13 (2, 60)	6 (1, 44)	2 (1, 21)		4 (1, 43)

Table 2. KM estimates (with 95% CI) of the risk of SNAE/death by tertiles of the ratios and years from starting ART

	5-year			10-year			15-year		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
LMR (log-rank p<0.0001)									
0.14-3.00	7.5%	(3.7-11.3)							
3.01-4.59	1.7%	(0.0-3.4)							
4.60+	9.0%	(2.3-15.7)							
NLR (log-rank p<0.0001)									
0-1.25	6.5%	(5.5-7.6)		12.0%	(10.3-13.6)		17.9%	(15.1-20.7%)	
1.26-2.05	6.4%	(5.3-7.4)		12.2%	(10.5-14.2)		19.5%	(16.8-22.9)	
2.06+	8.8%	(7.6-10.0)		14.2%	(12.4-16.4)		23.9%	(20.6-26.8)	
PLR (log-rank p=0.01)									
0.91-93.2	7.9%	(6.7-8.9)		14.0%	(12.4-15.7)		23.1%	(20.0-26.2)	
93.3-142.9	5.5%	(4.6-6.5)		9.9%	(8.3-11.4)		17.7%	(14.8-20.6)	
143.0+	8.0%	(6.9-9.3)		14.0%	(12.2-15.9)		19.2%	(16.4-21.9)	

Figure 1. Adjusted Hazard ratios (AHR) of Death, AIDS/Death, SNAE/Death from fitting standard Cox regression models with time-fixed covariates

