

The Neutrophil/Lymphocyte Ratio as a Potential Biomarker of Cardiovascular Disease Risk in HIV Positive Patients on Suppressive Antiretroviral Therapy

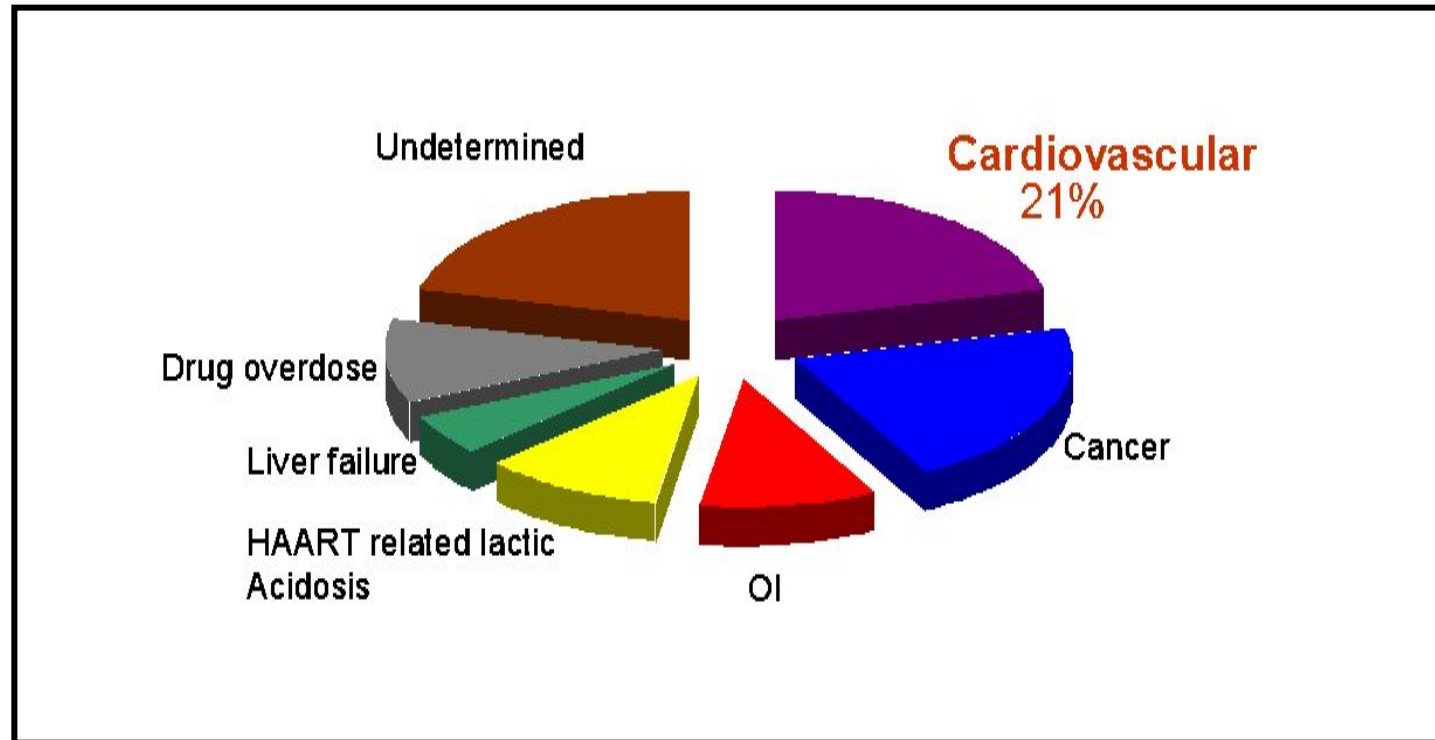
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**THE QUEEN'S
MEDICAL CENTER**

'Hawaii Aging with HIV Cohort' Study

Causes of death over 5 years in HIV+ patients



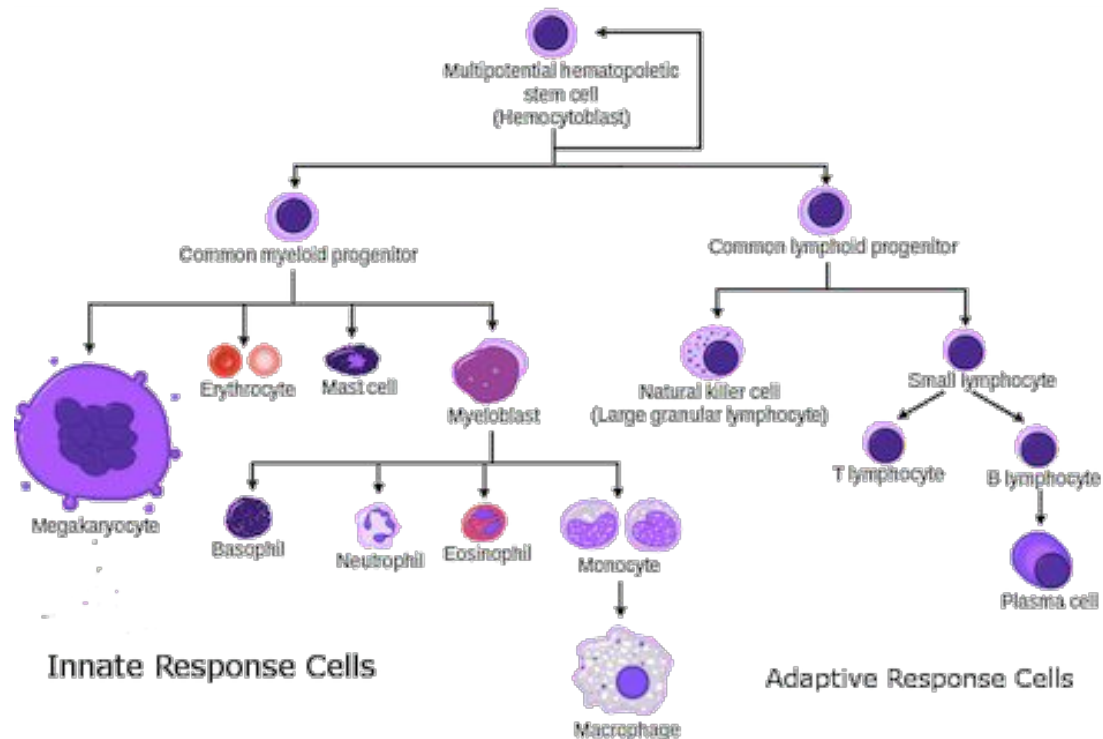
HIV+: 23 deaths among 250 individuals
HIV-: 2 deaths among 250 individuals

Need for Predictor of CVD Risk

- White blood cell count
- Neutrophil count
- Lymphocyte count
- Neutrophil/Lymphocyte Ratio

Neutrophil/Lymphocyte Ratio

- Neutrophils → Innate, Lymphocytes → Adaptive
- Increased Neutrophil Count leads to inflammation
- Decreased anti-inflammatory factors leads to decreased Lymphocyte Count



Associations with Neutrophil/Lymphocyte Ratio



Neutrophils

Lymphocytes

Increased ratio associated with CVD events such as:

- ❑ Increased long-term mortality in patients with ischemic and nonischemic heart failure
- ❑ Peripheral arterial disease
- ❑ Cardiac mortality in patients with stable coronary artery disease
- ❑ Left atrial thrombus

What about the HIV-infected population?

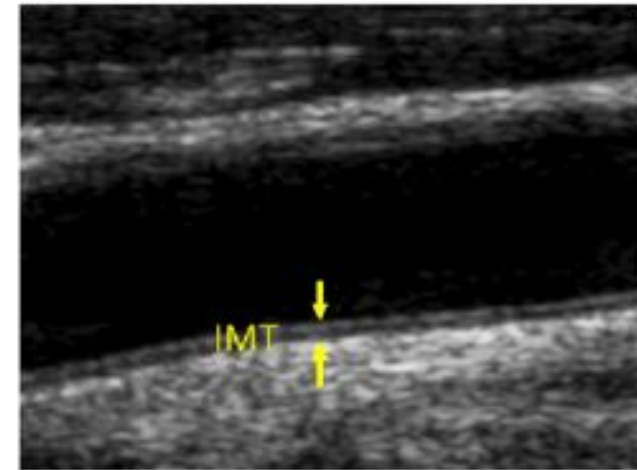
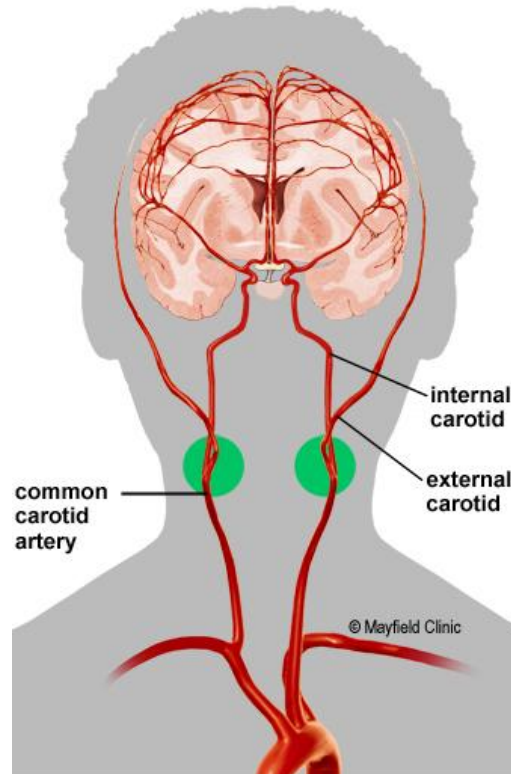


needed a surrogate marker
of CVD risk

Predictor of CVD

Carotid Intima-Media Thickness (CIMT)

- Predicts CVD events (> 1 , abnormal)
- Non-invasive, uses B-mode ultrasound
- IMT = distance between blood-intima interface and media-adventitia interface



Hypothesis

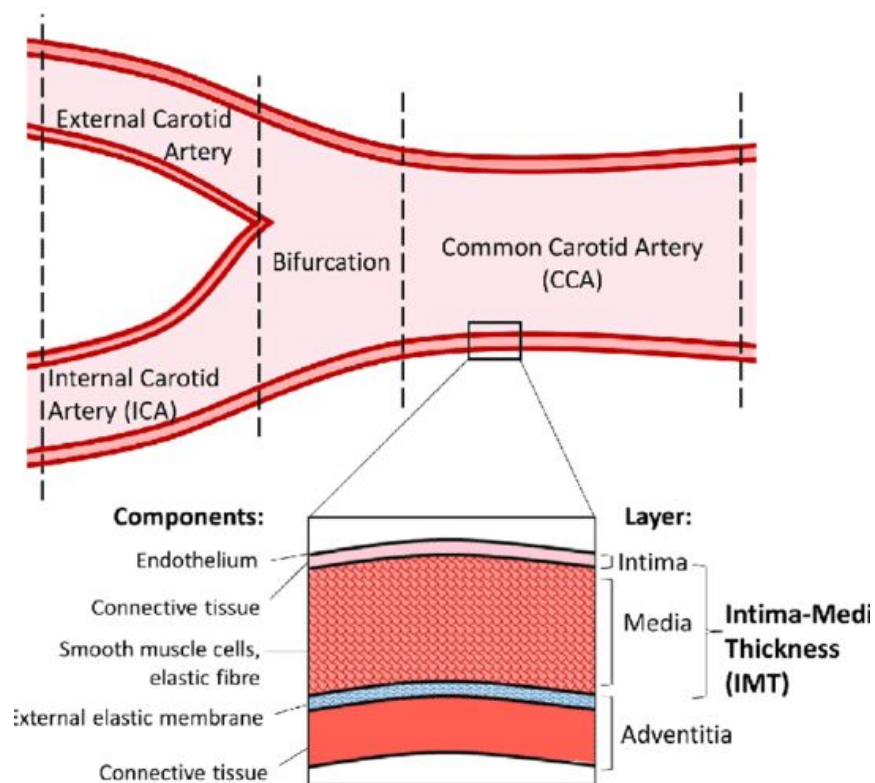
Neutrophil/Lymphocyte Ratio will be positively correlated with CIMT in HIV group on suppressive antiretroviral therapy

Recruitment

- 72 HIV-positive patients living in Hawaii
 - ≥ 40 years old
 - On ART w/ <20 copies/mL HIV RNA six months prior to enrollment
- 72 HIV-negative participants selected from similar backgrounds

Measurements

- Comprehensive HIV & cardiac evaluation
 - HIV history, CVD history, fasted blood counts
- CIMT measurements analyzed at USC by a single reader
 - Far wall of right distal common carotid artery and bifurcation



Spearman's correlation among Neutrophil/Lymphocyte Ratio, RCCA IMT, and RBIF IMT

		NLR	RCCA IMT	RBIF IMT
HIV +	RCCA IMT	-0.166 0.164		
	RBIF IMT	-0.200 0.093	0.586 0.000	
		NLR	RCCA IMT	RBIF IMT
HIV -	RCCA IMT	0.121 0.319		
	RBIF IMT	0.200 0.096	0.662 0.000	

Linear Regression of RBIF IMT on Neutrophil/Lymphocyte Ratio, Age, Gender, Ethnicity, Systolic Blood Pressure, and Total Cholesterol/LDL Cholesterol

NLR adjusted for:	HIV +		HIV –	
	Standardized Coefficients Beta	p-value	Standardized Coefficients Beta	p-value
Age + Gender + Ethnicity + SBP + Total Cholesterol	-0.278	0.018	0.052	0.672
Age + Gender + Ethnicity + SBP + LDL Cholesterol	-0.269	0.023	0.057	0.645

Our Results vs. Literature

- Negative correlation b/t CVD risk and Neutrophil/Lymphocyte

Ratio in HIV + cohort

VS.

- Positive correlation in general population
- Positive correlation in HIV + pop. in Italian study

Comparison of Studies

Quiros-Roldan, et al Study

- Mean age: 38.1 years
- 60.1% on ART
- 45% <37 copies/mL HIV RNA

3.05 Hazard Ratio

(p-value = 0.019)

comparing $NLR \geq 1.2$ to $NLR < 1.2$
in predicting CVD event incidence

Our Study

- Median age: 59 years
- 100% on ART
- 100% <20 copies/mL HIV RNA

-0.27 coefficient

(p-value = 0.023)

between RBIF IMT and NLR
after adjustment

Driver of Negative Association?

Neutrophil Count

Spearman's correlation among Lymphocyte Count, RCCA IMT, and RBIF IMT in HIV Positive Participants

		L	RCCA IMT
HIV +	RCCA IMT	0.123 0.302	
	RBIF IMT	0.149 0.211	0.553 0.000

Spearman's correlation among Neutrophil Count, RCCA IMT, and RBIF IMT in HIV Positive Participants

		N	RCCA IMT
HIV +	RCCA IMT	-0.086 0.475	
	RBIF IMT	-0.238 0.044	0.553 0.000

Spearman's correlation among Absolute Neutrophil Count, CCL2, CRP, D Dimer, IL6, and TNF alpha in HIV + cohort

	Neutrophil Count	CCL2	CRP	D Dimer	IL6
CCL2	0.065 0.590				
CRP	0.315 0.007	0.151 0.204			
D Dimer	0.087 0.467	0.302 0.010	0.323 0.006		
IL6	0.245 0.038	0.249 0.035	0.185 0.120	0.329 0.005	
TNF alpha	0.070 0.557	0.377 0.001	0.137 0.251	0.473 0.000	0.438 0.000

Limitations

- Cross sectional study (no causality)
- Small sample size
- High rate of male participation, lacking generalizability
- Used surrogate marker of CVD risk

Conclusions

- Hypothesis refuted
- Neutrophil Count driver; correlated with CRP and IL6 in HIV positive group
- No association in HIV negative group
- Future directions → investigate role of ethnicity, age, and length of time on ART on association

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Citations

- Kim, Stephanie, Melissa Eliot, Devin C. Koestler, Wen-Chih Wu, and Karl T. Kelsey. “Association of Neutrophil-to-Lymphocyte Ratio With Mortality and Cardiovascular Disease in the Jackson Heart Study and Modification by the Duffy Antigen Variant.” *JAMA Cardiology* 3, no. 6 (June 1, 2018): 455–62.
<https://doi.org/10.1001/jamacardio.2018.1042>.
- Ebrahim Shah, Papacosta Olia, Whincup Peter, Wannamethee Goya, Walker Mary, Nicolaides Andrew N., Dhanjil Surinder, et al. “Carotid Plaque, Intima Media Thickness, Cardiovascular Risk Factors, and Prevalent Cardiovascular Disease in Men and Women.” *Stroke* 30, no. 4 (April 1, 1999): 841–50.
<https://doi.org/10.1161/01.STR.30.4.841>.
- Shikuma, Cecilia, and Chow, Dominic. “Hawaii Aging with HIV Cardiovascular Study, 2009–2014.” Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2016–03–10.
<https://doi.org/10.3886/ICPSR36389.v1>
- Shah Anoop S.V., Stelzle Dominik, Lee Kuan Ken, Beck Eduard J., Alam Shirjel, Clifford Sarah, Longenecker Chris T., et al. “Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV.” *Circulation* 138, no. 11 (September 11, 2018): 1100–1112.
<https://doi.org/10.1161/CIRCULATIONAHA.117.033369>.
- Quiros-Roldan E, Raffetti E, Donato F, et al. Neutrophil to Lymphocyte Ratio and Cardiovascular Disease Incidence in HIV-Infected Patients: A Population-Based Cohort Study. *PLoS One*. 2016;11(5):e0154900. Published 2016 May 5. [doi:10.1371/journal.pone.0154900](https://doi.org/10.1371/journal.pone.0154900).
- Spine, Mayfield Brain &. “Carotid Stenosis, Carotid Artery Disease | Cincinnati, OH Mayfield Brain & Spine.” Accessed June 18, 2020. <http://www.mayfieldclinic.com/pe-carotidstenosis.htm>.

Questions?

