

CD4/CD8 Ratio, Age, and Serious Non-Infectious Outcomes in HIV-Infected Adults

Jessica L. Castilho¹, Megan Turner¹, Sally Bebawy¹, Bryan E. Shepherd², and Timothy R. Sterling¹
Division of Infectious Diseases¹ and Department of Biostatistics², Vanderbilt University School of Medicine, Nashville, TN

Introduction

- The non-infectious diseases (NCDs) of cardiovascular disease (CVD), cancer, cirrhosis, and renal disease increasingly contribute to excess morbidity and mortality in HIV-infected adults on antiretroviral therapy (ART)¹.
- CD4/CD8 ratio of HIV-infected patients on ART correlates measures of immune senescence and has been inversely associated with risk of NCDs in case-control studies²⁻⁴.
- The effect of age upon CD4/CD8 ratio and its predictive utility of NCDs in HIV-infected adults has not been described.

Methods

- We performed a retrospective cohort study of 1,700 HIV-infected adults who enrolled in care at the Vanderbilt Comprehensive Care Clinic between 01/1998 and 12/2010, initiated ART, and had documented HIV RNA <400 copies/mL for 1 year based upon at ≥ 2 lab values.
- Study follow-up time began at earliest time point of meeting inclusion criteria ("baseline").
- Serious NCD outcomes included incident CVD events (coronary artery disease or myocardial infarction, peripheral vascular disease, and cerebrovascular events), non-AIDS defining malignancies (excluding BCC and SCC skin cancers), cirrhosis, diabetes, and stage IV or V chronic renal failure.
- CD4/CD8 ratio trends among patients with persistent virological suppression after 3 years were analyzed by linear regression (n=454).
- Multivariable Cox proportional hazard models for the composite outcome of CVD or cancer were stratified by age.
- Modified Cox models in sensitivity analyses were restricted to only CVD outcomes.

Contact Information:

Jessica L. Castilho, M.D. M.P.H.
Vanderbilt University Medical Center
A2200 Medical Center North
1161 21st Avenue South
Nashville, TN 37232
jessica.castilho@vanderbilt.edu

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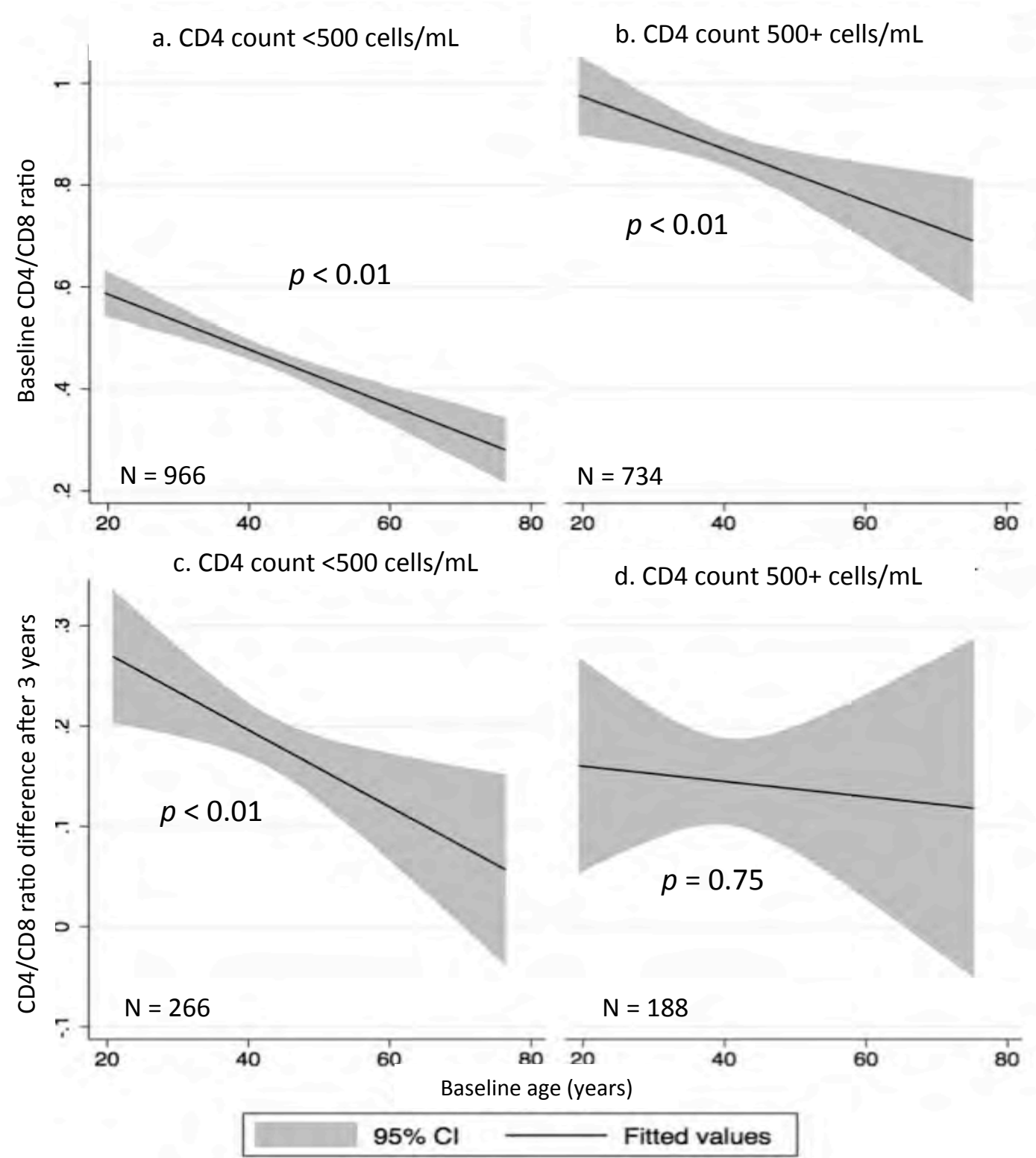
Results

Table 1. Patient baseline characteristics by CD4/CD8 ratio

	Low CD4/CD8 ratio < 0.4	Middle CD4/CD8 ratio 0.4-0.69	High CD4/CD8 ratio ≥ 0.7	P value for low vs. high groups
N (%)	538 (32)	558 (33)	604 (36)	
Age in years, median (IQR)	44 (38-50)	41 (34-48)	40 (32-46)	< 0.01 ^a
Male sex (%)	465 (86)	430 (77)	423 (70)	< 0.01 ^b
Non-white race (%)	223 (42)	235 (42)	249 (41)	0.94 ^b
HCV infection (%)	91 (17)	75 (13)	86 (14)	0.21 ^b
History of NCD (%)	9 (2)	11 (2)	6 (1)	0.31 ^b
CD4 count, median (IQR)	279 (189-391)	459 (364-592)	640 (496-843)	< 0.01 ^a
Total ART in years, median (IQR)	1.5 (1.1-3.3)	1.5 (1.1-3.0)	1.4 (1.1-3.1)	0.10 ^a
Calendar year, median (IQR)	2006 (2004-2009)	2007 (2004-2009)	2006 (2003-2009)	0.60 ^a
Study follow-up time in years, median (IQR)	3.1 (1.3-5.3)	2.8 (1.2-5.1)	3.1 (1.3-5.6)	0.70 ^a

^a Wilcoxon rank sum test; ^b χ^2 test

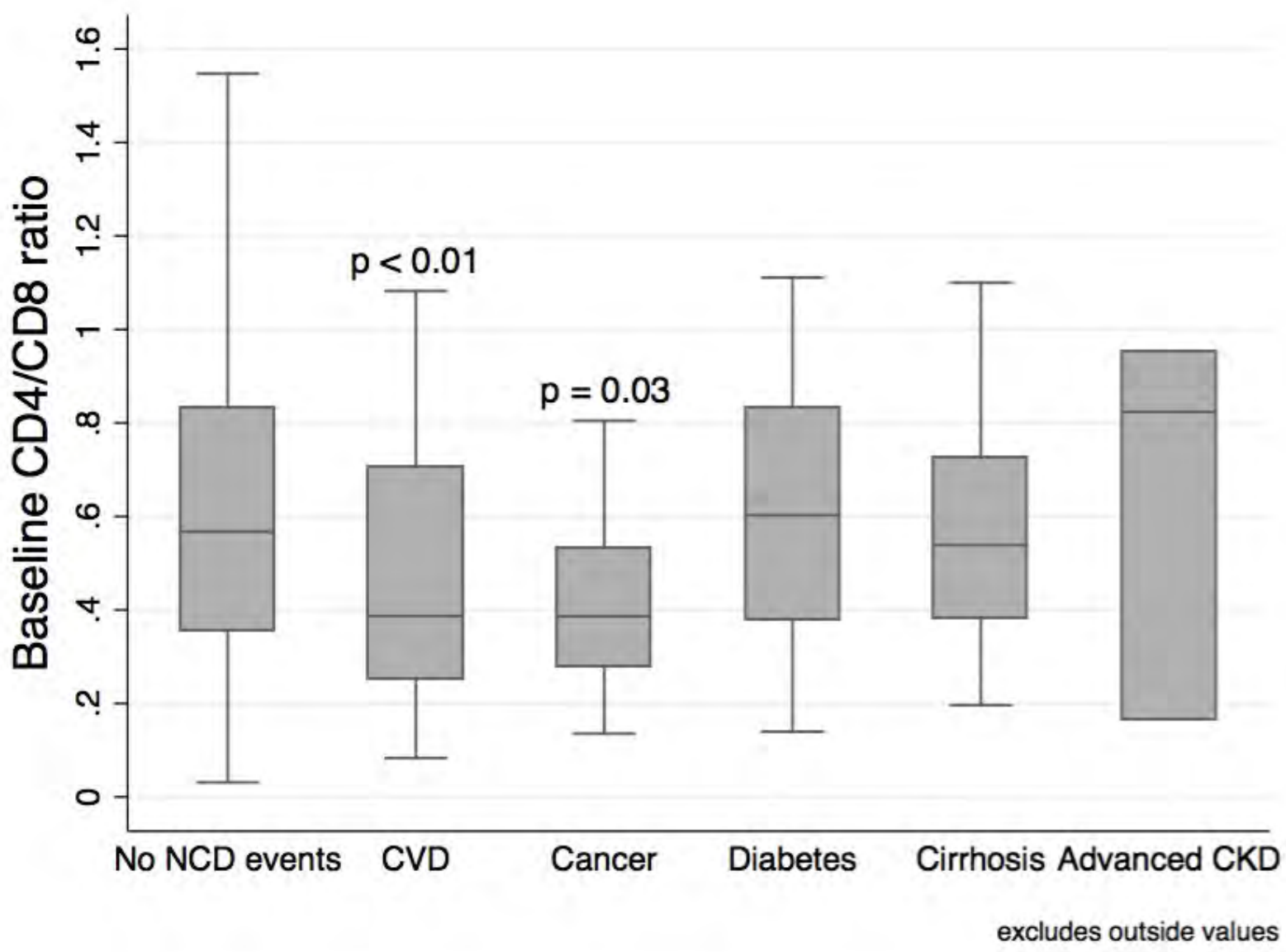
Figure 1. Trends in CD4/CD8 ratio and change in CD4/CD8 ratio by age, stratified by baseline CD4 count



NCD outcomes among all patients during follow-up (N=1,700):

- Any CVD event or diagnosis = 42 patients (2.5%)
 - Coronary artery disease events = 30 patients (1.8%)
 - Cerebrovascular disease = 9 (0.4%)
 - Peripheral vascular disease = 5 (0.3%)
- Non-AIDS-defining cancers = 28 patients (1.7%)
- Cirrhosis = 21 patients (1.2%)
- Diabetes = 21 patients (1.2%)
- Stage IV or V chronic renal failure = 3 patients (0.2%)

Figure 2. CD4/CD8 ratio of patients by NCD outcomes



P values reflect comparison with CD4/CD8 ratio among patients without any NCD events. Only CVD and cancer were significant.

Table 2. Univariate and multivariable Cox proportional hazard models for composite CVD or cancer outcome (n=65 events)

	HR	95% CI	p value	aHR	95% CI	p value
CD4/CD8 ratio, per 0.1 increase	0.85	0.78-0.93	< 0.01	0.90	0.81-1.00	0.05
Age, per 10 years	2.06	1.96-2.61	< 0.01	1.94	1.51-2.50	< 0.01
CD4 count, per 100 cells/mL	0.85	0.76-0.95	< 0.01	1.00	0.87-1.14	0.98
Female sex	0.45	0.21-0.94	0.03	0.60	0.28-1.27	0.18

- After stratifying by age, CD4/CD8 ratio only remained associated with CVD or cancer events for patients aged less than 50 years (aHR = 0.89, 95% CI 0.79-1.01).
- In sensitivity analyses, CD4/CD8 ratio remained associated with CVD outcomes alone (n=42 events) after adjusting for age and CD4 lymphocyte count in patients aged less than 50 years (aHR = 0.84, 95% CI 0.71-1.00).

Conclusions

- Independent of CD4 lymphocyte count, CD4/CD8 ratio was inversely correlated with age among similarly-treated HIV-infected adults.
- Among patients with consistent HIV viral suppression and CD4 lymphocyte count < 500 cells/mL, age was inversely associated with CD4/CD8 ratio improvement over time. There was no effect by age on CD4/CD8 improvement among those with CD4 lymphocyte count ≥ 500 cells/mL, highlighting the need for early ART in older adults.
- In time-to-event analyses adjusting for age, sex, and CD4 lymphocyte count, CD4/CD8 ratio was inversely associated with risk of serious CVD and cancer outcomes.
- The association was strongest among patients aged <50 years and those with CVD outcomes, suggesting an interaction between age and CD4/CD8 ratio on risk of atherosclerosis in HIV-infected adults on ART⁵⁻⁷.

Limitations & Future Directions

- This single-site study requires examination in larger observational cohorts where the effect of age on CD4/CD8 ratio over time and independent effects of age and CD4/CD8 ratio on risk of specific NCDs can be validated.
- We used CD4/CD8 ratio at a single time point due to the time-varying confounders that affect both CD4/CD8 ratio and NCD risk. Advanced statistical models and prospective data will be necessary to analyze the use of CD4/CD8 as a time-varying, clinical biomarker for risk of CVD events.

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