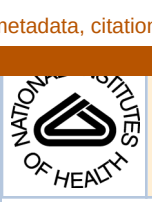

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Predictive Accuracy of the Veterans Aging Cohort Study (VACS) Index for Mortality with HIV Infection: A North American Cross Cohort Analysis

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC) or those of the Veterans Affairs.

Abstract

Background—By supplementing an index composed of HIV biomarkers and age (Restricted Index) with measures of organ injury, the Veterans Aging Cohort Study (VACS) Index more completely reflects risk of mortality. We compare the accuracy of the VACS and Restricted Indices 1) among subjects outside the Veterans Healthcare System (VA), 2) over 1–5 years of prior exposure to antiretroviral therapy (ART), and 3) within important patient subgroups.

Methods—We used data from 13 cohorts in the North American AIDS Cohort Collaboration (NA-ACCORD, n=10, 835) limiting analyses to HIV-infected subjects with at least 12 months exposure to ART. Variables included demographic, laboratory (CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine and hepatitis C status), and survival. We used C statistic and net reclassification improvement (NRI) to test discrimination varying prior ART exposure from 1–5 years. We then combined VA (n=5,066) and NA-ACCORD data, fit a parametric survival model, and compared predicted to observed mortality by cohort, gender, age, race, and HIV-1 RNA level.

Results—Mean follow-up was 3.3 years (655 deaths). Compared with the Restricted Index, the VACS Index showed greater discrimination (C statistic: 0.77 vs. 0.74; NRI 12%; $p<0.0001$). NRI was highest among those with HIV-1 RNA<500 copies/ml (25%) and age ≥50 years (20%). Predictions were similar to observed mortality among all subgroups.

Conclusion—VACS Index scores discriminate risk and translate into accurate mortality estimates over 1–5 years of exposures to ART and for diverse patient subgroups from North American

Keywords

HIV; Aging; Prognosis

With the advent of effective antiretroviral therapy (ART), the spectrum of disease experienced by those with HIV infection has changed. Viral suppression is common[1] and incident AIDS defining events are rare.[2] Yet, those with HIV infection continue to experience excess mortality [3;4] which is incompletely described by age, CD4 count, and HIV-1 RNA alone.[5]

Despite ART, chronic HIV infection appears to exacerbate generic pathophysiologic processes associated with aging which increase physiologic vulnerability relative to demographically similar uninfected individuals.[6–8] Consistent with current treatment guidelines[9], HIV providers routinely monitor general indicators of organ system injury including hemoglobin, platelets, aspartate and alanine transaminase (AST and ALT), creatinine, and viral hepatitis C infection (HCV) but have no index with which to integrate these data into an overall estimate of disease burden or mortality risk. Such a comprehensive measure would be useful as a means of more effectively motivating behavior change in the clinical setting[10], improved risk stratification in the analysis of observational data[11] and more effective randomized trials[12]. For example, indices such as the Framingham Risk Index has enhanced research and care in cardiovascular disease[13] and several geriatric risk indices are enhancing research and care for those aging without HIV infection.[14]

While the cumulative evidence supporting the accuracy and generalizability of the VACS Index exceeds that for any prior HIV risk index, the VACS Index builds upon important prior research.[15–22] Most prior indices emphasized AIDS defining conditions, CD4 cell count, and HIV-1 RNA. Some recognized the importance of age and anemia[16;20]. However much has changed since these indices were developed and validated. Specifically, the increasing role of multi-organ system injury (reflected by FIB 4, eGFR, and hemoglobin)

and of hepatitis C infection (HCV), and the decreasing role of AIDS Defining Illnesses, CD4 count, and HIV-1 RNA. By including FIB-4, HCV, eGFR, hemoglobin and age, and placing less weighting upon CD4 count and HIV-1 RNA, the VACS Index better reflects more of the major common pathways of physiologic injury among those on antiretroviral therapy. As a result, the Veterans Aging Cohort Study Index (VACS Index) discriminates risk of mortality more effectively than an index restricted to CD4 count, HIV-1 RNA and age (Restricted Index).[23 24]

Importantly, the discrimination of the VACS Index rivals that of indices in clinical use including the Framingham Index[13] and those recommended for use among geriatric patients.[14] Nevertheless, prognostic indices developed in one sample (those within the Veterans Affairs Healthcare System (VA)) may not generalize to a new sample or important subgroups.[25] Further, indices effective at one particular point in clinical care (ART initiation) may not generalize beyond treatment initation.[25] We use data from the North American AIDS Cohort Collaboration (NA-ACCORD) to test the generalizability of the VACS Index outside the VA and at differing intervals of exposure to ART. We then combine data from NA-ACCORD and VA to translate index scores to an estimated absolute risk of mortality and compare predicted to observed mortality by cohort and subgroups defined by sex, age, race, and HIV-1 RNA titer.

METHODS

Study Population

NA-ACCORD has been described in detail.[26–28] It is a multi-site collaboration of interval and clinical cohort studies in the United States and Canada, and represents the North American region of the International epidemiologic Databases to Evaluate AIDS (IeDEA). VACS has also been described in detail.[29] Although VACS is a participating cohort within NA-ACCORD, we separated VACS patients from the NA-ACCORD for this analysis to demonstrate the generalizability of our findings outside the Veterans Healthcare Administration.

We used data from 13 NA-ACCORD cohorts that routinely collect and contribute the laboratory data required for construction of the VACS Index. All included cohorts monitor deaths at local sites and regionally using death registries. United States cohorts also check for deaths using national registries (Social Security Administration or National Death Index). Among these cohorts, eligible subjects were HIV-infected individuals on ART for at least 1 year from 2000–2007 (n=15,938). Of these, 10,835 (68%) had complete data after 12 months of ART (90 days before to 180 days after) and constituted our sample with full data (complete cases). Using the same eligibility criterion, 5,066 VACS subjects were available for analyses. Both VACS and NA-ACCORD studies are approved by affiliated institutional review boards.

VACS and Restricted Index Scores

The development and internal validity of the VACS Index has been described (Table 1).[30] It includes age and routinely monitored laboratory tests: CD4 count, HIV-1 RNA, hemoglobin, platelets, AST, ALT, creatinine, and HCV status. Composite markers of liver and renal injury (FIB-4 and eGFR) are computed. FIB-4, composed of AST, ALT, platelets, and age, has been validated as an indicator of liver fibrosis [FIB-4=(years of age × AST)/(platelets in 100/L × sqrt of ALT.[31] eGFR composed of serum creatinine age, gender, and race, was included as a validated indicator of impaired renal function [eGFR=186.3 × (creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 for women) × (1.21 if Black)].[32] HCV status was defined as positive if the patient ever had a positive antibody test or detectable virus prior to the anchoring point

of our analysis (12 months of ART). Points are added to calculate score. The Restricted Index was developed solely for the purposes of comparing the accuracy and generalizability of an index restricted to CD4 count, HIV-1 RNA, and age with that of a more completely specified index. All predictors are categorized according to previously established cut points.[5;31–34]

Statistical Analysis

Statistical analyses were conducted by S Modur, JP Tate, and S Gange. Using the point system described above, VACS and Restricted Index scores were assigned to each subject at 1, 2, 3, 4, and 5 years of ART exposure. We evaluated the discrimination of the indices at these anchoring points. Observation time ended at death or was censored at the date of last follow-up, December 30, 2007 (administrative censoring) or five years from each anchoring point, whichever came first. For Year 1, labs were obtained −90 to +180 days of the anchor date; and +/− 180 days for years 2 to 5. These 5 anchors were then used to assess and compare discrimination of the indices using Cox proportional hazards models and Harrell's C-statistics (C statistic) among NA-ACCORD subjects only. We also measured C statistics among NA-ACCORD subjects after stratifying by sex (men, women), age (<50 years, ≥50 years), race (White, Black, and Hispanic), and HIV-1 RNA (<500 copies/ml, ≥500 copies/ml). Proportion of NA-ACCORD subjects reclassified by VACS Index compared with Restricted Index was calculated using the method by Cook, et al. (Appendix).[35;36]

Of 15,938 eligible NA-ACCORD subjects, 32% were missing at least one required laboratory value and were excluded from the complete case analyses. Those with complete data differed from those with missing data on gender, race, injection drug use (IDU), hemoglobin, platelets, AST, ALT, and FIB-4. We applied multiple imputation methods to the entire NA-ACCORD sample; results were similar compared to the complete case analyses (Appendix).

To translate scores to predicted mortality with maximal precision, we combined NA-ACCORD and VA subjects and fit a parametric (Gamma) regression model predicting all cause mortality using VACS Index score as the only predictor. This model provided an equation for calculating predicted mortality over 1–5 years for each value of the VACS Index score (Figure 1). Five year mortality predictions were compared graphically with observed mortality among NA-ACCORD and VA subjects separately and among designated subgroups. For each five-point interval of score (collapsed if necessary to maintain at least 5 deaths and 10 survivors in each interval), a Kaplan-Meier (KM) mortality estimate and 95% confidence interval were calculated.

RESULTS

Characteristics of the Population

The NA-ACCORD sample (n=10,835) included 2,982 women, 2,407 people ≥50 years, and 3,557 Black individuals. After one year of ART, 77% of the entire sample had HIV-1 RNA < 500 copies/ml, 34% had hemoglobin values between 12–13.9 g/dL, 10% had hemoglobin values between 10–11.9 g/dL, 25% had FIB 4 consistent with fibrosis (>3.25), 6% had stage III renal insufficiency (eGFR <60mL/min), and 24% had HCV co-infection (Table 1). The overall mortality was 1.6 per 100 person years. Median scores were 16 with a 1%-99% range of 0–80 for the VACS Index and 10 with a range of 0–71 for the Restricted Index.

Prognostic Accuracy in NA-ACCORD

Among NA-ACCORD subjects overall, the VACS Index was more discriminating of all cause mortality than the Restricted Index (Table 2, C statistic: 0.77 vs. 0.74) and among men

and women; Whites, Blacks and Hispanics; those < and ≥50 years of age; and those with HIV-1 RNA< and ≥ 500 copies/mL ($p<0.0001$ in all cases). Discrimination of the Restricted Index declined with increased prior ART exposure (C statistics: 0.74 at 2-year anchor; 0.72 at 5-year anchor), whereas discrimination of the VACS Index remained strong (C statistics: 0.79 at 2 years; 0.81 at 5 years). When compared with the Restricted Index, the VACS Index resulted in the reclassification of 53% of patients: 22% to a higher risk group and 31% to a lower risk group. The net gain in reclassification proportions at 5 years were 9% for survivors and 3% for those who died for a Net Reclassification Improvement (NRI) of 12% ($p<0.0001$). NRI was 25% among those with undetectable HIV-1 RNA and 20% among those 50 years and over. When 5-year Kaplan Meier observed mortality estimates were graphed, the VACS Index demonstrated a finer gradation of risk for more patients and a wider range of observed mortality compared with the Restricted Index (Figure 1a–b).

When components of the VACS Index were evaluated separately and in combination in NA-ACCORD and VACS cohorts (Table 3) we found that age alone offered modest risk discrimination (C stat: 0.56, 0.59 respectively). HIV biomarkers were more discriminating in NA-ACCORD than VACS data (c stat: 0.72, 0.67). Organ system biomarkers were less discriminating in NA-ACCORD than VACS data (c stat: 0.70, 0.75). When age, HIV biomarkers and organ system biomarkers were combined, discrimination was improved in both cohorts (c stat: 0.78 for both).

Calibration of Model Predictions Using Combined NA-ACCORD and VA Data

When a parametric survival model was calculated (Figure 2), predicted mortality was similar to observed mortality at 5 years for both NA-ACCORD and VA subjects (Figure 3 a and b) and when stratified by important subgroups (Figure 3c–j).

DISCUSSION

The VACS Index provided a more discriminating prediction of all cause mortality among HIV-infected subjects from North America on ART than the Restricted Index. This was true overall, with increasing exposure to ART, and among important subgroups, most notably among persons with low HIV-1 RNA and those ≥50 years of age—two rapidly growing populations in treatment. Based on established criteria,[13;25] the VACS Index has demonstrated excellent generalizability and is likely to accurately predict mortality among HIV-infected patients on ART in North America. Importantly, after demonstrating that this translation is accurate in demographically and clinically diverse subgroups, we provide a table and nomogram (Table 1 and Figure 2) and a website (http://vacs.med.yale.edu) to facilitate calculating VACS Index scores and translating them to predicted mortality rates. Potential applications for the VACS Index include patient management and clinical research.

C statistics are a commonly employed metric for evaluating the discrimination of prognostic indices.[37] In uncensored data, the C statistic is the likelihood that, if any two subjects were drawn from the sample, the subject with the higher score would die before the subject with the lower score. Although these categories are somewhat arbitrary, C statistics between 0.50–0.59 are considered poor; 0.60–0.69, fair; 0.70–0.79, good; 0.80–0.89 very good; and above 0.89, excellent.[14] While Restricted Index C statistics ranged from 0.63–0.76 (“fair” to “good”), VACS Index C statistics ranged from 0.70 to 0.81 (“good” to “very good”). Discrimination was particularly better among those with undetectable HIV-1 RNA (C statistics: 0.67 vs. 0.74) and those over 50 years of age (C statistics: 0.63 vs. 0.70). C statistics for the VACS Index for all cause mortality meet or surpass those reported for prognostic indices used in clinical practice including the Framingham Index for predicting

Cardiovascular Disease and validated indices predicting all cause mortality among aging uninfected individuals.[13;38;39]

A newer metric, developed and popularized by the methodologists working on the Framingham Risk score, is the net reclassification improvement (NRI)[35;36]. This is calculated by separating those who died and those who lived and asking in each group whether the VACS Index resulted in a change in risk classification compared with the Restricted Index. Among those who died, a higher risk classification is considered an improvement and a lower risk classification is considered an error. Among those who lived, a lower risk classification is considered an improvement and a higher classification is an error. The NRI is the sum of the differences. The net gain in reclassification proportions at 5 years was 9% for survivors and 3% for those who died for an overall statistic of 12% ($p<0.0001$). Further, the NRI was even higher among those with undetectable HIV-1 RNA (25%) and those 50 years and over (20%). These NRIs suggest a highly clinically significant improvement in discrimination[36;40] and are greater than improvements seen by the addition of D-dimer to the VACS Index.[24]

For maximal clinical and research utility, providers and investigators need a means of translating VACS Index scores to mortality risk. We combined NA-ACCORD and VACS data to provide as precise a translation as possible. We then considered the accuracy of this translation by cohort and among important subgroups. Because such translations depend upon the overall mortality rate in the cohort,[13;25;38] we conducted this work among cohorts with uniform access to regional and/or national death registries. In these analyses, the predicted mortality based upon VACS Index score was similar to observed mortality among veteran (VACS) and nonveteran (NA-ACCORD) subjects; and among: men and women; Black and non-Black patients; those <and ≥50 years old; and those with HIV-1 RNA < and ≥ 500 copies/ml.

To understand how the VACS Index reclassifies risk, consider an HIV-infected 45-year-old man who, after 12 months of ART, has a CD4 count of 500 cells/mm^3 and an undetectable HIV-1 RNA but is HCV co-infected with a FIB-4 >3.25. He, like one in four NA-ACCORD subjects, was assigned 0 points by the Restricted Index with a 2% predicted 5-year mortality. Using the VACS Index, he was assigned 5 points for HCV co-infection and 25 points for his FIB-4 value for a score of 30 and an predicted 5-year mortality of 12%. Fifty-three percent of NA-ACCORD subjects assigned a score of 0 by the Restricted Index were assigned a higher score by the VACS Index.

Having an accurate, generalizable, responsive, and feasible method for estimating individual risk can improve effectiveness and efficiency of chronic disease management in major ways[41–43]. First, it can inform decision making when an intervention puts the patient at some immediate risk for longer term gain[44;45]. This is true whenever patients are asked to undergo a risk of immediate harm from treatment in the hope of averting long term disease incidence or progression-- commonly the case in cancer screening and primary and secondary prophylaxis for cardiovascular disease and stroke. It is also true when considering aggressive treatment protocols (toxic chemotherapy, organ transplant, or major surgery) for cancer or heart disease. Second, it can motivate patients to modify health behaviors such as adherence to medication, smoking, diet, exercise, and alcohol use by quantifying the impact these changes have on risk and by charting progress after modifying risk[46–50]. Third, it can identify patients in need of intensive management either with respect to site of care (outpatient, inpatient, intensive care unit, skilled nursing facility, nursing home) or care management (case management, frequency of follow up).

Of note, none of these applications require that index identify all modifiable sources of risk, only that it accurately, generalizably, responsively, and feasibly estimate risk of mortality—including risk associated with the modifiable factors of interest.[25;39] Because many sources of modifiable risk have a similar common pathway to physiologic injury, it is not efficient or feasible for a single index to include all modifiable sources of risk. Instead, separate analyses can map changes in risk score associated with changes in modifiable factors of interest. We are currently undertaking a series of analyses demonstrating this for adherence to ART, alcohol use, smoking, and substance use, but these are beyond the scope of this paper.

The VACS Index also predicts cardiovascular mortality[51], hospitalization and medical intensive care unit admission[52] and is correlated with functional performance[53] and fragility fractures[54]. It offers an improved means of balancing patient enrollment by severity of illness in randomized trials and of controlling for disease severity in observational analyses, and it may eventually prove a useful intermediate outcome for interventional and observational research. Because the discrimination of the VACS Index for mortality is maintained over extended prior exposure to ART it also offers a means of charting a patient's progress over time.

Although the utility of the VACS Index for clinical management can only be established through a randomized trial comparing management with and without the Index, evidence to date suggests that it offers useful insight. We have previously shown that hemoglobin, FIB-4, and eGFR, as well as CD4 count and HIV-1 RNA, change substantially in response to ART initiation, not always in the same direction,[33] and that the VACS Index is more responsive to ART initiation and differing levels of ART adherence than the Restricted Index.[33] Third, we have shown that the VACS Index is more correlated with biomarkers of inflammation (IL-6), microbial translocation (D-dimer), and hyper coagulability (sCD14) than the Restricted Index.[5] Taken together, these data suggest that the VACS Index provides a more comprehensive means of tracking disease burden, including the effects of chronic inflammation, over time.

Further, to facilitate use of the VACS Index in the clinical setting, we have developed a web site calculator accessible via smart phone or computer with an automatic conversion of the VACS Index score to a risk estimate (HTTP://VACS.MED.YALE.EDU). The site includes regularly updated links to supporting evidence for the index. As we develop information regarding how behavior change alters risk we will include this information as an additional link for the calculator. We also provide SAS programming for any who wish to include the calculation as part of their electronic medical record system or for analyses of grouped clinical data (WWW.VACOHORT.ORG).

Our analysis has substantial strengths. We demonstrated the generalizability of the VACS Index in a large, independent sample on ART, over differing periods of ART exposure and among important subgroups of patients.[25] By combining NA-ACCORD and VA samples we were powered to precisely translate VACS Index scores to predicted mortality and to consider whether predicted mortality matched observed deaths overall and among important subgroups. Further, the VACS Index is based on laboratory tests currently ordered in the course of routine management and therefore offers enhanced clinical insight requiring only that providers calculate and interpret the score. We have simplified this process by providing a web site and smart phone calculator (http://vacs.med.yale.edu). Eventually the Index could be calculated by the clinical laboratory (or the electronic medical record) every time component tests are ordered, as is current practice for eGFR.

A limitation of any large observational study is missing data. While subjects with missing values in NA-ACCORD tended to have more liver disease and less anemia, the imputed analyses yielded results similar to complete cases (Appendix), suggesting that missing data did not compromise our findings. Further, the VACS Index may be improved in the future. Our choice of risk factors was based on prior work,[16;20;21;23;55] a desire to base the index on consistently measured metrics such as clinical laboratory tests, and the need to validate findings. As the population with HIV ages, higher age thresholds will likely become relevant. Of note, we have evaluated whether: BMI, lipid profiles, smoking status, hypertension;[56] inflammatory biomarkers (D-dimer, IL-6, and soluble CD14)[24], and functional status[57] improve the discrimination of the VACS Index. While many of these predict mortality in unadjusted analyses, VACS Index scores co vary with these factors. When added to the VACS Index, only D-dimer and/or sCD14 resulted in risk reclassification that exceeded 1%. Additional factors (such as D-dimer) may be added to the VACS Index in the future if they can be consistently measured and they improve discrimination sufficiently to justify added cost and complexity.[13;36]

In summary, we have demonstrated that a novel index composed of routine clinical data can predict mortality among HIV-infected individuals on ART with good to very good discrimination and consistent calibration across important subgroups. Measures of general organ system function included in the VACS Index substantially enhance discrimination. While it would be a reasonable precaution to verify the calibration of the VACS Index among younger patients and subjects outside North America, predicted mortality from the VACS Index is likely generalizable to HIV-infected individuals over 30 years of age in care in North America. Among these individuals, the VACS index is ready for clinical and research application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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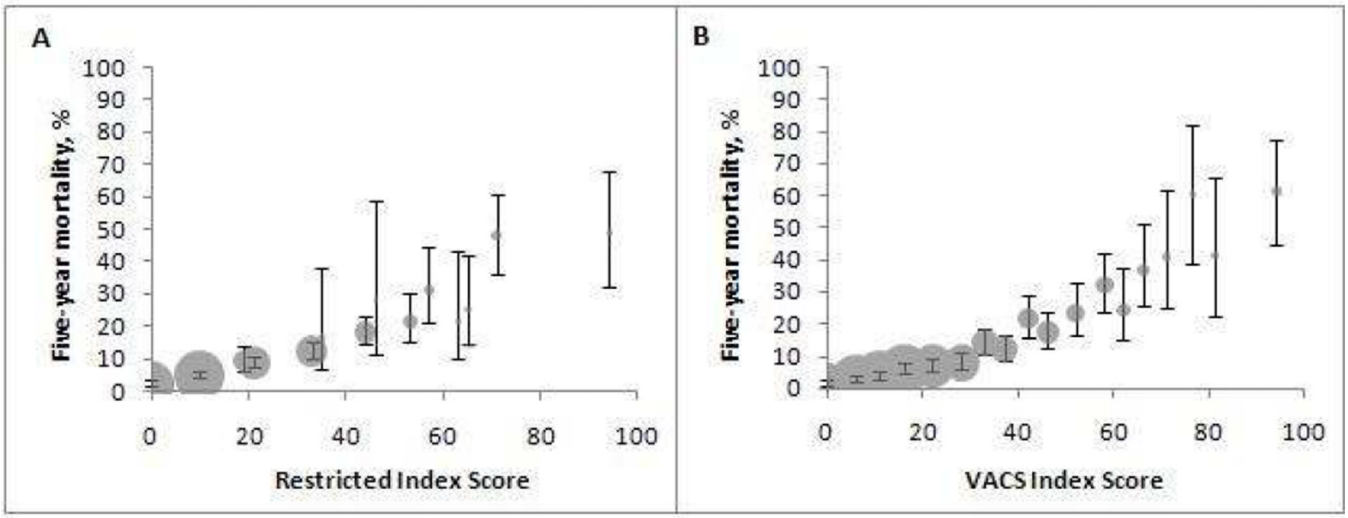

Figure 1.

Observed (Kaplan-Meier estimates) five-year mortality according to index score in 10,835 HIV infected patients after one year of antiretroviral therapy. The I bars denote 95% confidence intervals. Bubble size is proportional to the number of subjects at each data point. (NA-ACCORD Subjects Only)

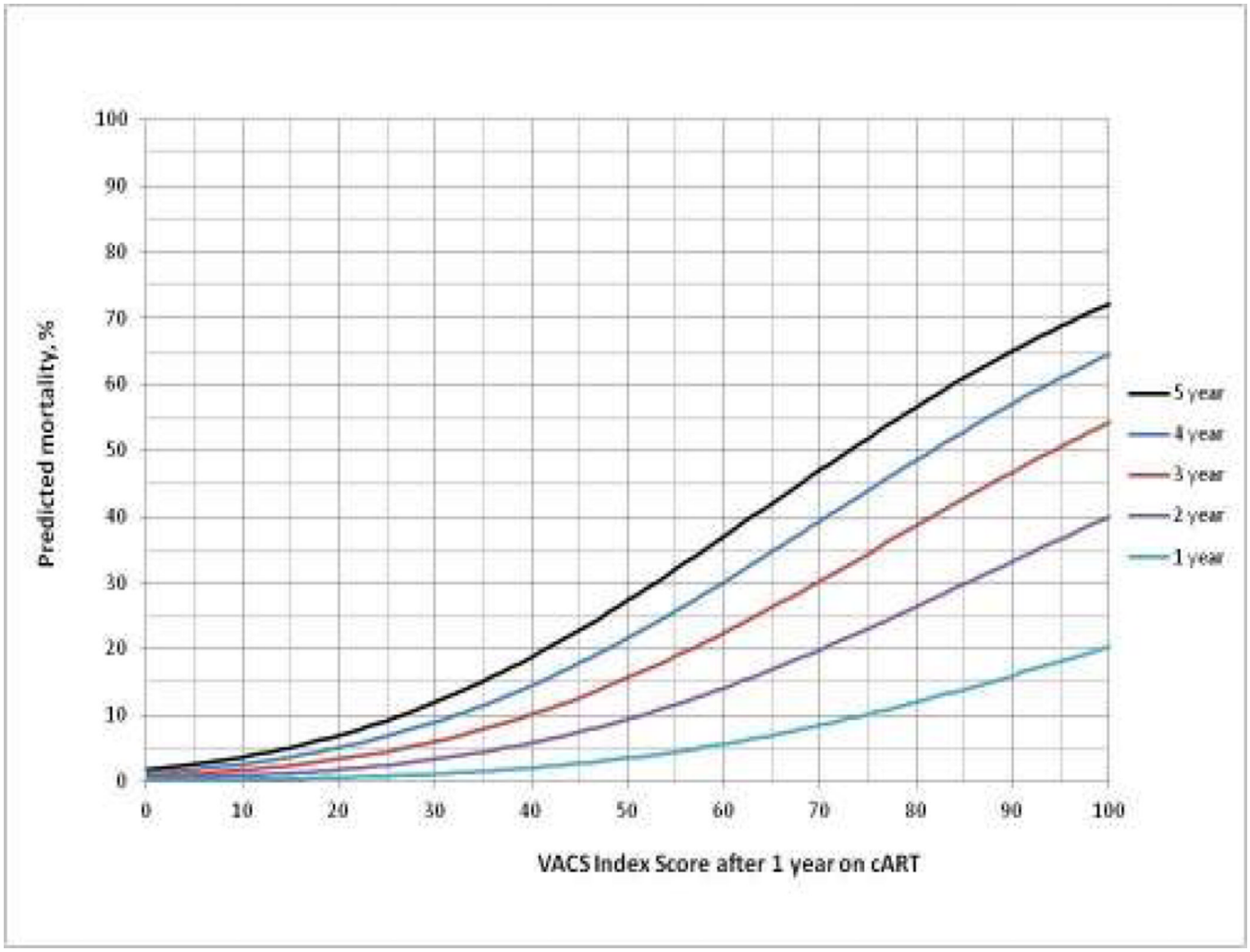

Figure 2.
Predicted mortality by VACS Index score based on 15,901 HIV infected patients with one year of antiretroviral therapy (ART). (NA-ACCORD and VACS Subjects)

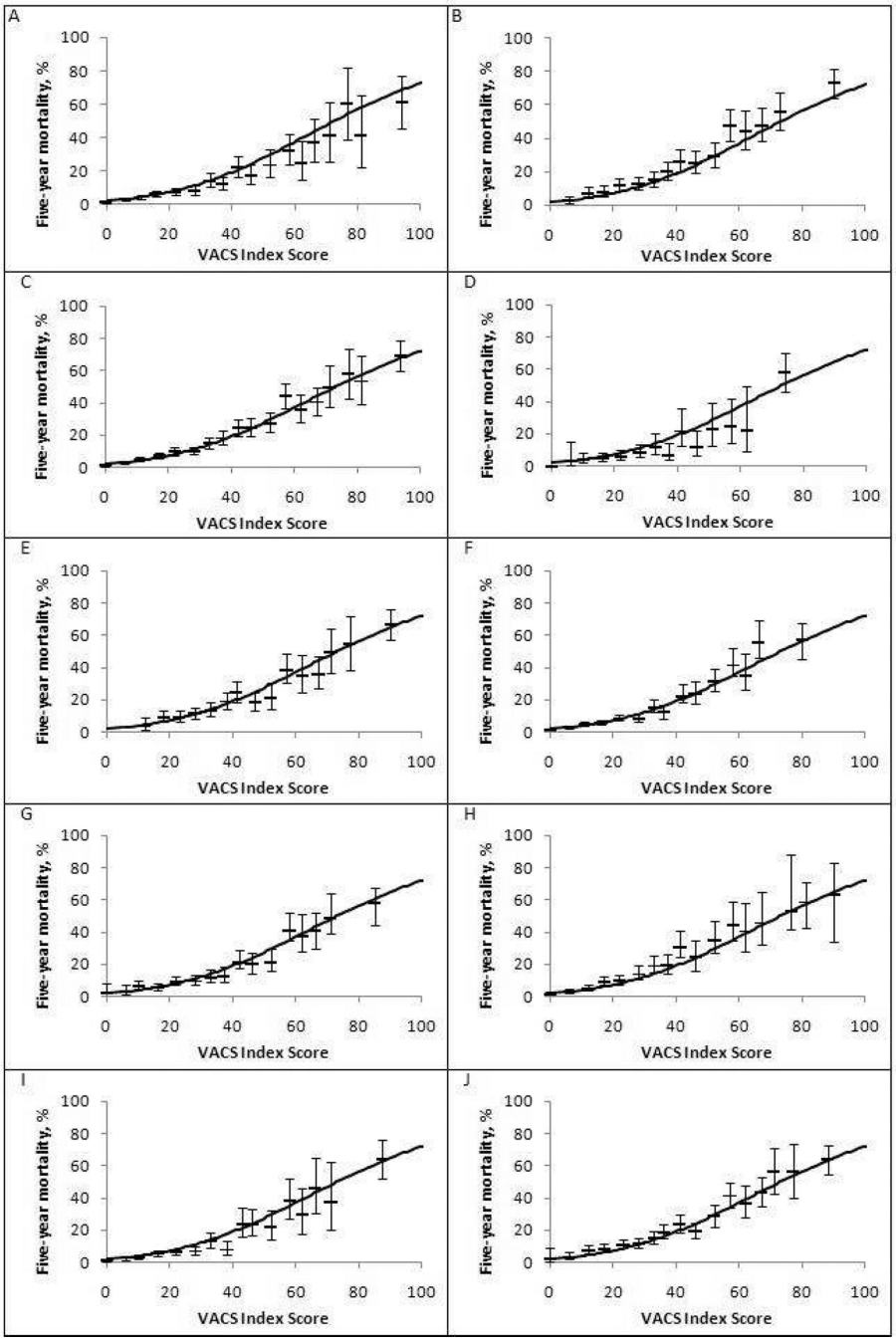

Figure 3.

Kaplan-Meier estimates of five-year mortality according to VACS Index score after one year of antiretroviral therapy, by subgroup. (NA-ACCORD and VACS Subjects)
A. NA-ACCORD (N = 10835), B. VACS (N=5066) C. Men (N = 12785), D. Women (N = 3116), E. Age < 50 years (N = 11191), F. Age >50 years (N = 4710), G. Black (N= 5878), H. White (N = 6079), I. HIV RNA <500 copies/ml (N=8715), J. HIV RNA > 500 copies/ml (N= 7186). The I bars denote the 95% confidence intervals. Solid line is fitted curve for the overall study sample (N = 15901).

Table 1

Components of the Restricted and VACS Indices, showing point values assigned and distribution of selected characteristics in 10,835 HIV positive patients (NA-ACCORD subjects only).

		Points Assigned		Distribution	
Component	**Level**	**Restricted Index**	**VACS Index**	**N**	**%**
Age (years)	<50	0	0	8428	(78)
	50 to 64	23	12	2245	(20)
	≥ 65	44	27	162	(2)
CD4 (cells/mm^3)	≥ 500	0	0	3789	(35)
	350 to 499	10	6	2443	(23)
	200 to 349	10	6	2660	(25)
	100 to 199	19	10	1293	(12)
	50 to 99	40	28	346	(3)
	< 50	46	29	304	(3)
HIV-1 RNA (copies/ml)	< 500	0	0	8324	(77)
	500 to 1×10^5	11	7	2161	(20)
	≥ 1×10^5	25	14	332	(3)
Hemoglobin (g/dL)	≥ 14		0	5897	(54)
	12 to 13.9		10	3720	(34)
	10 to 11.9		22	1062	(10)
	< 10		38	156	(1)
FIB-4	< 1.45		0	8103	(75)
	1.45 to 3.25		6	2213	(20)
	> 3.25		25	519	(5)
eGFR (mL/min)	≥ 60		0	10149	(94)
	45 to 59.9		6	430	(4)
	30 to 44.9		8	141	(1)
	< 30		26	115	(1)
Hepatitis C Co-Infection			5	2605	(24)

		Points Assigned		Distribution	
Component	**Level**	**Restricted Index**	**VACS Index**	**N**	**%**
Sex	Male			7853	(72)
Race	White			4723	(44)
	Black			3557	(33)
	Hispanic			1734	(16)
	Other			821	(7)
HIV Transmission by IDU				1721	(16)
Year of ART initiation, median (IQR)				2000	(1998–2003)
Person Years of Observation				35598	
Deaths					
Total				655	NA
In First 5 Years				571	NA

Table 2

Discrimination of the VACS and Restricted Indices for 5-year, all-cause mortality (NA-ACCORD subjects only)

		Restricted Index	VACS Index	p-value
Time on ART	1 Year	0.74	0.77	<0.0001
	2 Years	0.74	0.79	<0.0001
	3 Years	0.72	0.77	<0.0001
	4 Years	0.72	0.79	<0.0001
	5 Years	0.72	0.81	<0.0001
Sex	Male	0.76	0.77	<0.001
	Female	0.72	0.76	<0.001
Race	White	0.76	0.79	<0.001
	Black	0.71	0.74	<0.001
	Hispanic	0.70	0.77	<0.001
Age, years	<50	0.75	0.78	<0.001
	>= 50	0.63	0.70	<0.0001
HIV-1 RNA,	<500	0.67	0.74	<0.0001
copies/ml	>=500	0.7	0.71	<0.0001

Table 3

Incremental Discrimination of VACS Index Components in NA-ACCORD and VACS Cohorts (C statistic and 95% CI).

Components of VACS Index	NA-ACCORD		VACS	
Age	0.56	(0.54,0.58)	0.59	(0.57,0.61)
HIV Biomarkers (CD4, HIV1 RNA)	0.72	(0.70,0.75)	0.67	(0.64,0.69)
Organ System Biomarkers (Hgb, FIB4, eGFR, HCV)	0.70	(0.68,0.72)	0.75	(0.73,0.76)
Age + HIV Biomarkers (Restricted Index)	0.74	(0.72,0.77)	0.72	(0.70,0.74)
Age + Organ System Biomarkers	0.71	(0.69,0.74)	0.75	(0.73,0.77)
Complete VACS Index	0.78	(0.75,0.79)	0.78	(0.77,0.80)