Joint modelling of longitudinal and time-to-event data: An illustration using CD4 count and mortality in a cohort of patients initiated on antiretroviral therapy

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Abstract

Background: Modelling of longitudinal biomarkers and time-to-event data are important to monitor disease progression. However, these two variables are traditionally analyzed separately or time-varying Cox models are used. The former strategy fails to recognize the shared random-effects from the two processes while the latter assumes that longitudinal biomarkers are exogenous covariates, resulting in inefficient or biased estimates for the time-to-event model. Therefore, we used joint modelling for longitudinal and time-to-event data to assess the effect of longitudinal CD4 count on mortality.

Methods: We studied 4014 patients from the Centre for the AIDS Programme of Research in South Africa (CAPRISA) who initiated ART between June 2004 and August 2013. We used proportional hazards regression model to assess the effect of baseline characteristics (excluding CD4 count) on mortality, and linear mixed effect models to evaluate the effect of baseline characteristics on the CD4 count evolution over time. Thereafter, the two analytical approaches were amalgamated to form an advanced joint model for studying the effect of longitudinal CD4 count on mortality. To illustrate the virtues of the joint model, the results from the joint model were compared to those from the time-varying Cox model.

Results: Using joint modelling, we found that lower CD4 count over time was associated with a 1.3-fold increase in the risk of death, (HR: 1.34, 95% CI: 1.27-1.42). Whereas, results from the time-varying Cox model showed lower CD4 count over time was associated with a 1.2-fold increase in the risk of death, (HR: 1.17, 95% CI: 1.12-1.23).

Conclusions: Joint modelling enabled the assessment of the effect of longitudinal CD4 count on mortality while correcting for shared random effects between longitudinal and time-to-event models. In the era of universal test and treat, the evaluation of CD4 count is still crucial for guiding the initiation and discontinuation of opportunistic infections prophylaxis and assessment of late presenting patients. CD4 count can also be used when immunological failure is suspected as we have shown that it is associated with mortality.

Keywords: Time-to-event data; longitudinal data; joint models; CD4 count; mortality; bias

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed.

However, the manuscript can be downloaded and accessed as a PDF.

Figures

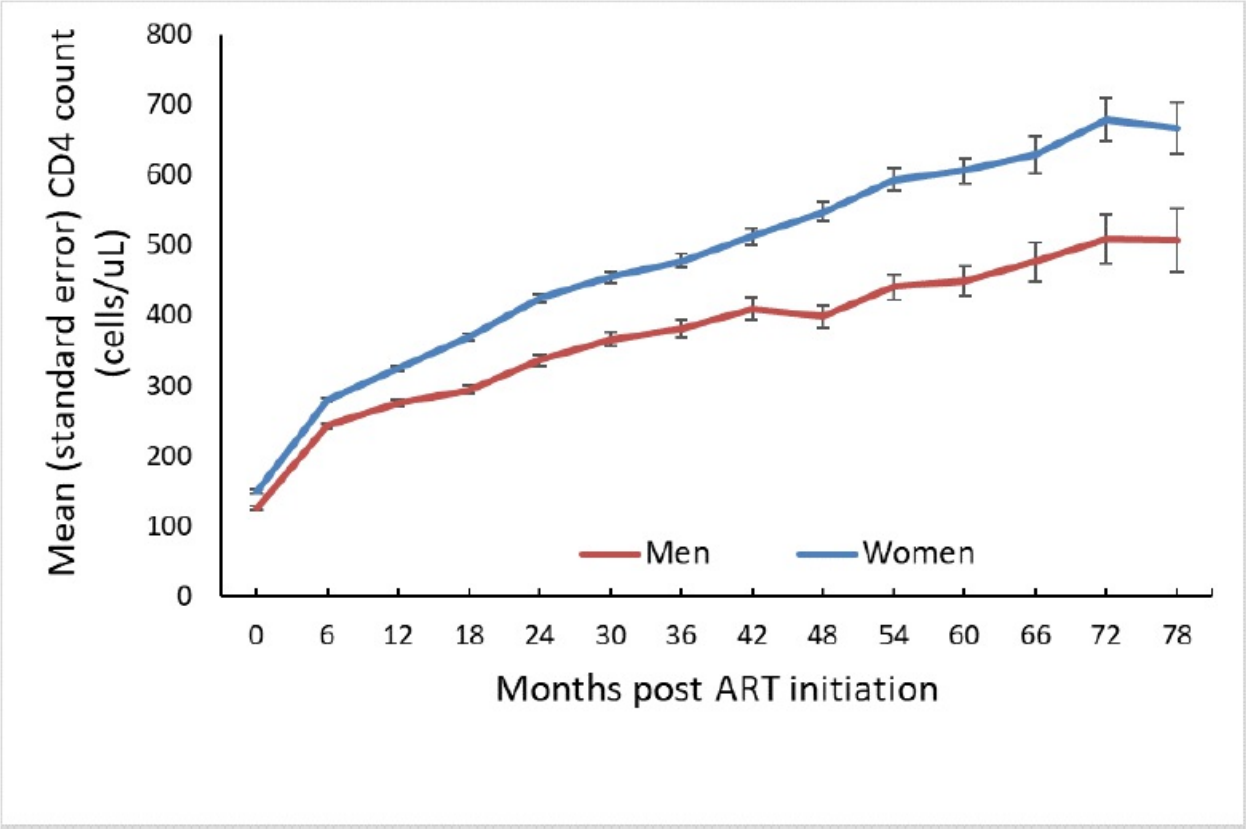
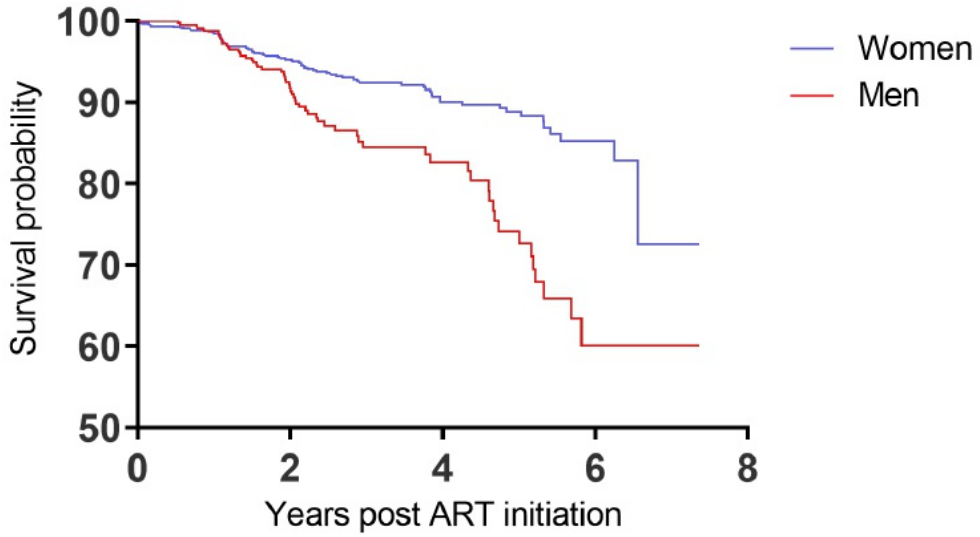


Figure 1

Mean CD4 count (cells/μL) over time by gender



Number at risk					
Men	555	283	77	13	0
Women	1091	625	211	40	0

Figure 2

Kaplan-Meier curve for survival