Testing mark-specific vaccine efficacy with missing marks

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This article develops hypothesis testing procedures for the stratified mark-specific proportional hazards model in the presence of missing marks. The motivating application is placebo-controlled preventive human immunodeficiency virus (HIV) vaccine efficacy trials, which have objective to test if the mark-specific relative hazard rate (vaccine versus placebo) is unity for all mark values, and to test whether it changes with the mark (the mark is the genetic distance of an infecting HIV sequence to an HIV sequence represented inside the tested vaccine). These tests inform on whether the vaccine affects the rate of HIV infection for any HIV genotype and whether the vaccine effect differs by HIV genotype, respectively, and guide vaccine development. One difficulty with these assessments is that the mark may be missing from many HIV infected subjects, predominantly due to rapid evolution of the infecting HIV. The test statistics are constructed based on a two-stage efficient estimator which utilizes auxiliary predictors of the missing marks. The asymptotic properties of the testing procedures are investigated. In addition, their finite-sample performances are investigated in simulations, which verify the double-robustness property under missing at random marks and demonstrate effectiveness of the predictive auxiliaries to recover efficiency. One of the simulations models the recent landmark trial in Thailand, which was the first trial to demonstrate partial efficacy of an HIV vaccine. The new methods are applied to the real data set.

Key Words: Competing risks failure time, HIV vaccine efficacy trial, augmented inverse probability weighted complete-case estimator, mark-specific vaccine efficacy