Exploring disease progression using a latent class approach for multiple longitudinal markers and event history: example with Multi-System Atrophy

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Abstract: Some diseases are characterized by numerous markers of progression. Although not specific to, this is particularly the case in neurodegenerative diseases where pathological brain changes may induce multiple clinical signs on which the progression of a patient is assessed. For instance, Multiple System Atrophy (MSA), a rare neurodegenerative synucleinopathy, is characterised by various combinations of progressive autonomic failure and motor dysfunction (parkinsonism and cerebellar ataxia), and by a very poor prognosis with a median survival of a few years after diagnosis. Describing the progression of such complex and multi-dimensional diseases is particularly difficult. One has to simultaneously account for the assessment of multivariate markers over time, the occurrence of clinical endpoints, and the highly suspected heterogeneity between patients which is partly due to the difficulty to formally diagnose the disease. Yet, such description is crucial for understanding the natural history of the disease, stage patients diagnosed with the disease, unravel subphenotypes, and predict the prognosis. Through the example of MSA progression, we show how a latent class approach can help describe complex disease progression measured by multiple repeated markers and clinical endpoints, and identify subphenotypes for exploring new pathological hypotheses.

Key words: Disease progression; Joint models; multivariate longitudinal data; Heterogeneity