Latent Markov Model for profiling heart failure patients' adherence to drugs

Laura Savaré[1,2,3], Nicole Fontana[1], Francesca Ieva[1,2]

1 MOX, Department of Mathematics, Politecnico di Milano, Milan, Italy
2 HDS, Health Data Science Center, Human Technopole, Milan, Italy
3 National Centre for Healthcare Research & Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy

Introduction: Cardiovascular diseases represent approximately one-third of the cause of mortality worldwide, where 85% of them were due to heart attack and stroke, as stated by authoritative sources [1]. The cornerstone of heart failure (HF) treatment is pharmacotherapy, and the most widely administered therapies are angiotensinconverting enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARBs) called as renin-angiotensin system (RAS) inhibitors, beta-blockers (BB) and mineralocorticoid receptor antagonist (MRA) [2]. Guidelines suggest the use of these therapies in combination since they have been shown to reduce mortality and morbidity in heart failure patients with reduced ejection fraction. Despite this, no attempts have been made to jointly explore the association between clinical outcomes and adherence to the polytherapy administered to these patients. This study focuses on the crucial notion of adherence to polytherapy and its dynamic nature. To tackle this aspect, we present a groundbreaking approach that uses Latent Markov models [3] to analyze the longitudinal data on drug purchases provided by an administrative database.

Aims: Our objective was to develop an innovative tool for assessing long-term drug adherence to polytherapy using a secondary database and examine its impact on patients' survival probabilities within a community-based cohort.

Methods: From the Lombardy healthcare administrative database, we analysed patients discharged after their incident heart failure between 2006 and 2012. A new method was introduced for measuring adherence to polytherapy over time, specifically targeting renin-angiotensin system inhibitors, beta-blockers and mineralocorticoid receptor antagonists. In particular, we define our latent Markov model using multivariate response variables that represent three levels of adherence to the three drugs commonly administered to HF patients each month throughout the first year of observation. Age, gender, and the multisource comorbidity score are examples of fixed and time-varying covariates that will affect the initial and transition probabilities of the latent process. A Cox regression model was used to determine the effect of patients' adherence on mortality, and a Restricted Mean Survival Time Analysis was implemented.

Results: The mean age of the cohort was 74.6 years; 48.4% was female; and the overall death rate was 29%. We fit different LMM with a different number of latent states, and the final model is chosen according to different measures and its interpretability, such as BIC and AIC, in our case with three latent states. The resulting LM model incorporates four latent states and includes individual covariates such as age, sex, and MCS. To interpret the latent process, we examine the probabilities of exhibiting a particular level of adherence to a single drug, given the latent state. We derived the following labelling for the latent states:

- Latent state 1: very-low willingness to be adherent to polytherapy
- Latent state 2: average willingness to be adherent to polytherapy
- Latent state 3: strong willingness to be adherent to RAS
- Latent state 4: strong willingness to be adherent to polytherapy

Where by willingness, we refer to an individual's tendency to take the drugs as prescribed or to follow medical indications to refrain from drug usage, thereby being labelled as a non-user of the drugs.
Nine latent behavioural profiles were identified from the latent process temporal order analysis. Profiles characterized by a progressive increase over time of adherence significantly lowered the mortality risk (hazard ratio 0.84; 95% confidence interval 0.78-0.90) compared to those consistently low adherent. In

Figure 1, a difference in the curves is observed when comparing patients who have the same latent state throughout the entire observation period. High-adherent patients have a greater probability of survival than those with moderate and very-low adherence. Patients always high-adherent to RAS (group C) and those always high-adherent to polytherapy (group D) show similar curves, with a slightly high probability of survival for those who take all drugs. These curves highlight that adherence to therapies is an important prognostic factor and that patients with higher adherence are more likely to survive than those with lower adherence, given the adjustments for age, sex and MCS. Moreover, at patients who consistently take their prescribed medication during the observation period have a considerable gain in years of life. The results revealed a significant positive difference in RMST between high-adherent (D) and low-adherent (A) patients. The estimate showed that patients who adhered to their prescribed therapies survived 0.831 (95%CI, [0.689, 0.973]) years longer, on average, than non-adopters when following up patients for seven years.
The results show that even a slight difference in adherence can significantly impact survival, emphasizing the need to educate patients on the importance of medication adherence and provide continuous support to improve their adherence.

Conclusions: We observe that different adherence behaviours lead to a different probability of survival and hospital readmission. This study underscores the importance of secondary prevention and continuous monitoring of heart failure patients to enhance patient's health and quality of life. These procedures are crucial for identifying areas of improvement and promoting better adherence to prescribed therapies.

References:

[1] World Health Organization. Cardiovascular diseases Fact sheet reviewed June 2021. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds), 2021. Accessed: 2023-03-27.

[2] McMurray JJ., Adamopoulos S., Anker SD, Auricchio A. et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847. doi: 10.1093/eurheartj/ehs104. Epub 2012 May 19. Erratum in: Eur Heart J. 2013 Jan;34(2):158. PMID: 22611136.

[3] Bartolucci F., Farcomeni A., Pennoni F. Latent Markov Models for Longitudinal Data. Chapman & Hall/CRC, Philadelphia, PA, January 2013. ISBN 9780429102578. doi: 10.1201/b13246.

Figure 1. Kaplan–Meier survival curves for overall survival stratified by four latent-behavioural profiles