Monitoring drugs-based therapeutic paths in heart failure patients

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Group 8

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Motivation and main objectives

Heart failure is a pathophysiological state in which the heart fails to supply the required amount of blood and oxygen to the body. In Europe, HF is the most common cardiovascular reason for hospitalization among adults and affects 1-2% of the population. Proper treatment may improve the symptoms of heart failure and may help some people live longer but 1 out of 2 patients with chronic diagnosis is non-adherent to drugs.

The focus of the study is on the **adherence** during the first year of observation which measures the obedience of the patient to the medical therapy.

The main **objective** is the development of an innovative method for **profiling patients based on** different **drug-utilization behaviors** focusing on the analysis of **polytherapy** and investigating the impact of such profiles on patients' overall **survival** and **rehospitalization**. The interest is also on the impact of adherence on **time-to-event** outcomes such as date of death and date of next hospitalization for the subjects.

Dataset description

This **administrative** database is in the form of **longitudinal** data. It contains information about 40'000 patients from Lombardy hospitalized for heart failure from 2006 to 2012, concerning both hospitalizations and pharmaceutical purchases. In particular, drugs are classified by Anatomical Therapeutic Chemical (ATC) code: anti-aldosterone **(AA)** agents, beta-blocking **(BB)** agents and renin angiotensin system **(RAS)** inhibitors. We **assumed** that the patient takes the drug **consecutively from the day of purchase.**

- Age
- Gender
- Comorbidities
- Dates of study
- Final condition

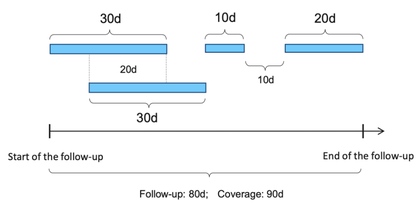
- Date of hospitalizations
- Length of stay

- Date of purchase
- ATC code
- Length of prescription

Measuring adherence

Adherence to a single drug can be measured with different metrics. One way is to use the **PDC** (Proportion of Days Covered) and can be computed in this way:

$$\text{PDC} = \frac{\text{number of distinct coverage days}}{\text{number of days in the observation period.}}$$



To evaluate polypharmacy, we introduced the PDC total which is a value that carries the information about the adherence to the three types of drugs.

Note that we **consider** only the **drugs** that have been **purchased** at least **once** from the patient. In order to explain how PDC total has been computed let's make an example: if the patient has never assumed drugs of type RAS and today he has taken drugs of type AA but not BB, the adherence for this day is 1/2. Another possible way to measure adherence is using **PAI** (Patient Adherence Indicator) computed as the ratio between PA and PI. PA is the number of pharmacological classes to which the patient is adherent at the defined threshold of 80% and PI is the number of drug types purchased at least once in the last year.

Type of drug	AA	BB	RAS
Usage	Take at least once	Never taken	Taken at least once
Adherence	0.83 ✓	/ ✗	0.69 ✗

→ PI=2, → PA=1 → PAI=0.5

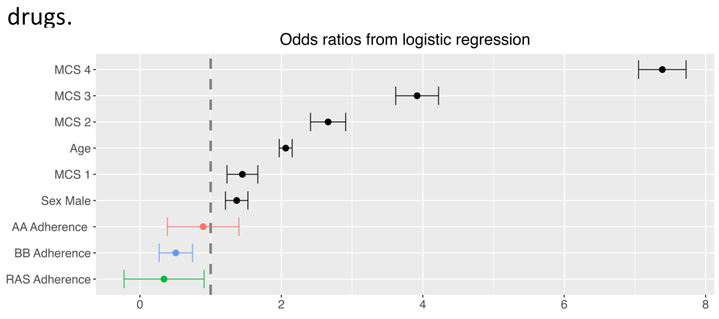
Logistic Regression

Single Drug

We were interested in understanding the efficacies of the different drugs, we focused only on patients that had a therapy composed of a **single drug**, and we set as adherent those that has a PDC of more than 80% (equivalent to PAI = 1).

The relevant covariates are the **age** (standardized), the **sex**, the **Multisource Comorbidity Score (MCS)**, a score from 0 to 4 reflecting the comorbidities of the patient extracted from the previous hospitalization and pharmacological history of the patients, considered as a **categorical** covariate.

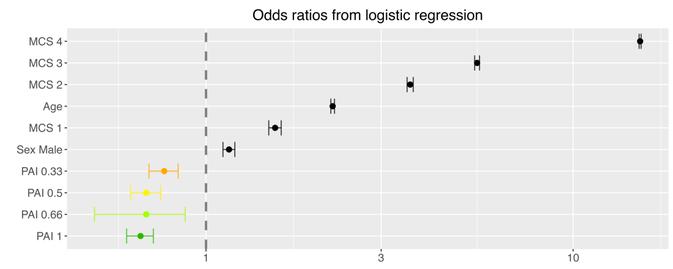
We discovered that there seems to be a hierarchy between the drugs.



Polypharmacy

The adherence was measured via the **PAI** in the first year computed on the specific prescribed therapy inferred from the purchase history. Both MCS and PAI were considered as **categorical covariates**, one category for each MCS score, and 5 categories for the PAI: 0, 0.33, 0.5, 0.66, 1, since we had therapies composed of at most 3 drugs. The reference classes are MSC 0 (healthy patient) and PAI = 0.

The model has a ROC AUC of 0.78, with an accuracy of 71%.

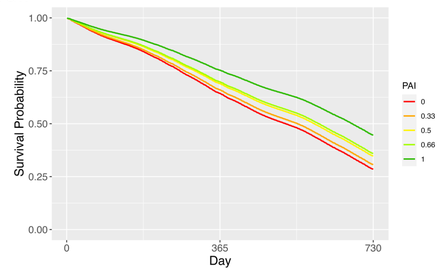


Survival Analysis

Polypharmacy

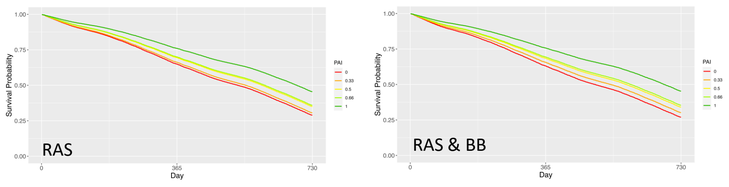
We performed a **survival analysis** to predict how the adherence to the prescribed therapy influenced the life expectancy of each patient. To fit such model, we used sex, age, MCS, time spent in hospital and PAI as features. In particular, five different categories were considered for the PAI: 0, 0.33, 0.5, 0.66, 1. By fitting a Cox proportional hazard model, it seems clear that **sex** is **not relevant** for the survival.

The first result is presented in the plot, where are shown the survival curves for patients that have all the three drugs in the therapy.



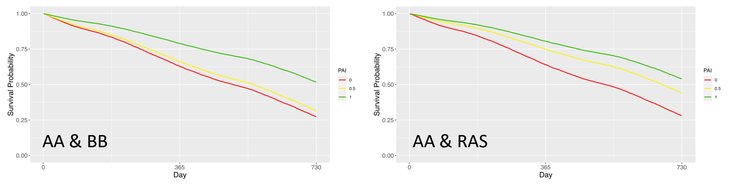
Further results

- The effect of BB is negligible if combined with RAS;



we can see that the BB drug does not give substantial improvements of the life expectancy, thus we might conclude that BB is quite useless if prescribed with RAS.

- In general, the combination of two drugs results in a more efficient therapy;



- It is evident that there exists a hierarchy among the three drugs: RAS seems to be more efficient than AA, which seems to be more efficient than BB.

Functional Data Analysis

Polypharmacy

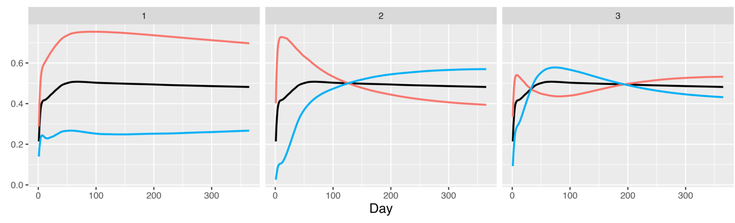
We needed a more complex descriptor of the patient's behaviour, therefore we decided to use a **functional** measure of the adherence and not a categorical one. We used a functional PDC (for both single drugs and polytherapy) which is a running average over time. Let's make an example for a single drug:

Day	1	2	3
Drug usage	✓	✗	✓
Functional PDC	1	0.5	0.66

In the case of polytherapy the ratio between taken and prescribed drugs in each day were averaged over time.

Principal component analysis

After having performed the smoothing we passed to the functional **principal component analysis**. This is a plot of the first three principal components that explain a cumulative variability of 77%, 93% and 97%.



The interpretation is clear: PC1 determines the global trend, PC2 discriminates between patients adherent at the beginning of the year and patients adherent at the end.

We then tried to separate the two groups (survived and not) using the scores of the first principal components but without success as the distributions are not separable.

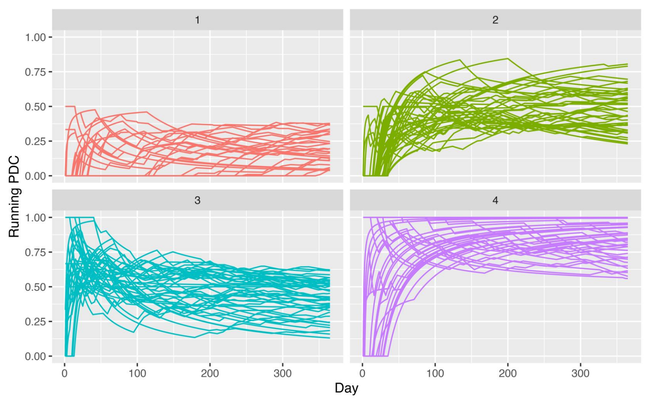
Subsequently, we used the first 3 PCAs in a logistic regression model (together with the features used in the categorical part). We have that the first two PCs are significant, the first was protective while the second was not, while the third was not significative.

Functional Clustering

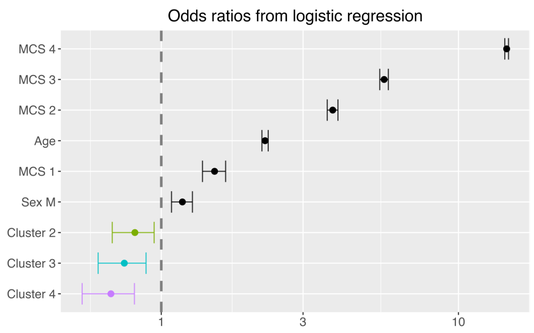
We performed functional clustering via **functional k-means**, using as metric the **L^2 distance**, using a **medoid** as centroids and **NO warping functions.** We obtained **4 clusters**:

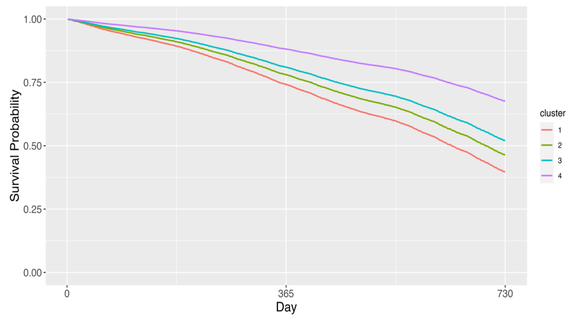
1) low adherence patients;
2) patients starting low but eventually following the treatment;
3) patients starting high but eventually falling off the treatment;
4) high adherence patients.

We used as **adherence measure** the **cluster** a patient belonged to, in order to capture the behaviour over time.



We then performed the same logistic regression and survival analysis as above, using the four clusters.





Discussion and Conclusions

- With both categorical and functional analysis, we demonstrated that **adherence** to a given therapy **affects positively** the patients' **survival** and time-to-death for the disease in question. Given this insight it could be useful to have the family doctor monitor closely the given patient to ensure a quite substantial reduction in mortality.
- With the functional approach we discovered that being **adherent at the beginning** has a significant effect on patients' survival probability and time-to-death. This result was possible since we used a time-varying measure of adherence and not a single value.
- We performed the same procedure outlined above also analyzing the **rehospitalization** in the first year: the relation with adherence was of the same kind but not as significant since there are many reasons that would result in a hospitalization of the patient, specifically given the age and comorbidity distribution of the cohort.

References

[1] *Corrao, Rea, Ghirardi, Soranna, Merlino, Mancia.* Adherence with antihypertensive drug therapy and the risk of Heart Failure in clinical practice.

[2] *Spreafico, Gasperoni, Barbati, Ieva, Scagnetto, Zanier, Iorio, Sinagra, Di Lenarda.* Adherence to Disease-Modifying Therapy in Patients Hospitalized for HF: Findings from a Community-Based Study.

[3] *Corrao, Rea, Di Martino, De Palma, Scondotto, Fusco, Lallo, Belotti, Ferrante, Addario, Merlino, Mancia, Carle.* Developing and validating a novel multisource comorbidity score from administrative data: a large population- based cohort study from Italy.