HEART FAILURES AND MIXED EFFECTS MODELS: QUALITY OF THE HOSPITALS AND SUPPORT TO DOCTORS' DECISIONS

Course of Applied Statistics - A.Y. 2021/22
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DATASET

Heart failure (HF) is a pathophysiological state in which the heart fails to supply required amount of blood and oxygen to the body.

HF is a common, costly, cronic and potentially fatal condition.
The risk of death is about 35% the first year after diagnosis, while by the second year less than 10% for those who remain alive
Because of this we take into account for each patient her/his information within three years since their first hospitalization.

HF is widespread all over the world, being the leading cause of both hospitalization and readmission amongst older adults (≥ 65).

The dataset [1] collects hospitalizations and medical histories from 2006 to 2012 in Lombardia. It includes patients' and hospitals' characteristics as well as information related to hospitalizations, such as clinical interventions, duration and diagnosis.
Our analysis does not consider pharmacological prescriptions, which are included in the dataset.

DATE of HOSPITALIZATION	Hosp. cause CODE	Hospital ID	Patient characteristics (unique CODE, SEX, date of birth, LHA)	STATUS at the end of the study, ENTRANCE/EXIT DATEs	Dummies for patient's comorbidities	Dummies for clinical interventions	Hospital stay LENGTH
				DEAD	[1,0,1,1,0..]	[0,0,0,1]	
				DEAD	[1,1,1,1,0..]	[0,0,0,0]	
				LOST	[1,0,0,0,0..]	[1,0,0,1]	
				LOST	[1,0,0,1,0..]	[1,0,1,1]	
				SURVIVED	[0,0,0,0,1..]	[0,0,0,1]	

RESEARCH QUESTIONS

- Do hospitals have different impact on patients' recovery?
- Can we help doctors making their decisions?
- Is it possible to predict a re-hospitalization?
- Can we help doctors estimating the prognosis?

FRAGILITY ANALYSIS

At first, we do a medical research analyzing the different diagnosis a doctor could make for a patient and then we assign a level of risk, from the least dangerous to the most, respectively 1 and 5, to each diagnosis.
After collecting the diagnosis in each hospitalization, we compute a grade to describe the situation of a patient using the following formula:

$$H = \{hospitalizations\}$$

$$Grade = \max_H\{level\ of\ risk\} + \mathbb{1}_{\{\sum_H level\ of\ risk\ \geq\ 10\}}$$

To verify the significance of this classification, we perform a one-way Manova test that confirms the presence of differences among groups in time spent in hospital and survival rate (Fig. 1-2).

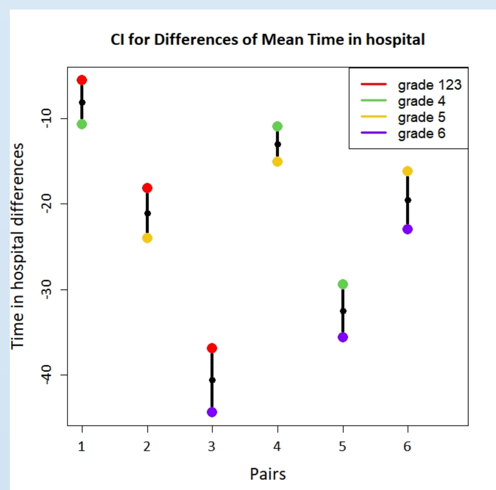

Fig. 1.

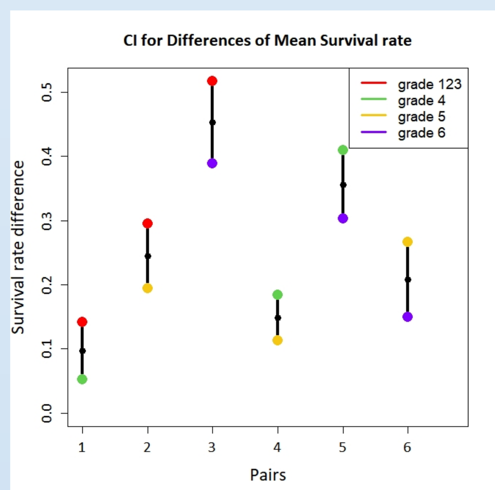

Fig. 2.

$$BonfCI_{1-\alpha}(\tau_{it} - \tau_{jt}) = \left[\overline{X_{it}} - \overline{X_{jt}} \pm t_{1-a/2k}(n-g) * \sqrt{\frac{S_{tt}}{n-g} * \left(\frac{1}{n_i} + \frac{1}{n_j}\right)} \right]$$

$$\begin{gathered} i,j = grade\ 123, 4, 5, 6 \\ t = time\ spent, rate\ survival \\ k = 12\ (Bonf.correction) \end{gathered} \qquad \overline{X_{it}} - \overline{X_{jt}} \sim \mathrm{N}\left(\tau_{it} - \tau_{jt}, \sigma_{tt}\left(\frac{1}{n_i} + \frac{1}{n_j}\right)\right)$$

The normality hypothesis is not verified, but the group means look very different.
Thanks to this fragility classification we can generalize the specific medical situation of each patient, reducing the medical complexity and the variety of diagnoses.

QUALITY OF HOSPITALS – LOGISTIC REGRESSION FOR SURVIVAL RATE

Since we have different features to describe the fragility and the risk situation of the patients, we move our attention to hospital treatments.
We select the hospitals which have a large volume of patients and starting from their overall situation, we consider, as statistical units, only patients who visited the same hospital.
For each patient we consider the information regarding three years since their first hospitalization, and we compute the fragility grade. We end up with 2500 patients and 144 hospitals.

Logistic Linear Mixed Effects Model

$$logit(y_{ij}) = \beta_0 + \beta_1 * \log(age_{ij}) + \beta_2 * \log(n°\ hospitalizations_{ij}) + \beta_3 * grade_{ij} + \beta_4 * interv_{ij} + \alpha_j$$

$$\boldsymbol{\alpha} \sim N(0, \sigma_b^2)$$

y_{ij}: survival indicator (1 alive, 0 dead) for patient i in hospital j
$interv$: clinical interventions (bypass, shock, defibrillator, angioplastic)
α_j: random intercept due to hospital j visited by patient i

Classification features of the model

A **ROC curve** (**receiver operating characteristic curve**) is a graph showing the performance of a classification model at all classification thresholds.

Sensitivity (true positive rate) refers to the probability of a positive test, conditioned on truly being positive.
Specificity (true negative rate) refers to the probability of a negative test, conditioned on truly being negative.

AUC stands for "Area under the ROC Curve".

RECALL

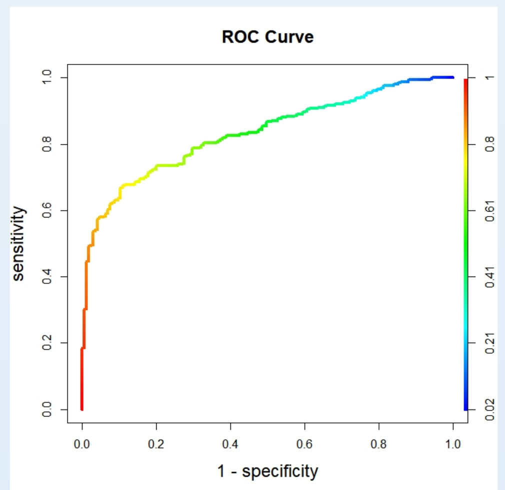

Fig. 3.

AUC: 0.83, Specificity: 0.80, Sensitivity: 0.73. (Fig. 3)
We prefer specificity over sensitivity: it's more important to know if a patient could die in order to give more attention to him. When we increase the threshold, we get higher specificity and lower sensitivity, as we are moving from blue to red on the ROC curve. We highlight the optimal point on the curve and it corresponds to a threshold of 0.70.
Our model seems to perform well, which means that the information in the first 3 years of a patient's medical history is key in predicting his survival rate.

Analysis of the random effect

The Variance Partition Coefficient is the analogous to PVRE index for logistic regression mixed models.

$$\mathbf{VPC} = \frac{\sigma_b^2}{\sigma_b^2 + \frac{\pi^2}{3}} = 0.06 \qquad \hat{\sigma}_b^2 = 0.203$$

The amount of variability the presence of the grouper (hospitals) accounts for is 6%.
Thanks to the dotplot (Fig. 4), points and intervals estimates for the random effects can be visualized. For each hospital, we can assess if the corresponding effect is positive or negative. This could be a powerful tool to evaluate the differences in terms of treatment offered by the medical institutions.

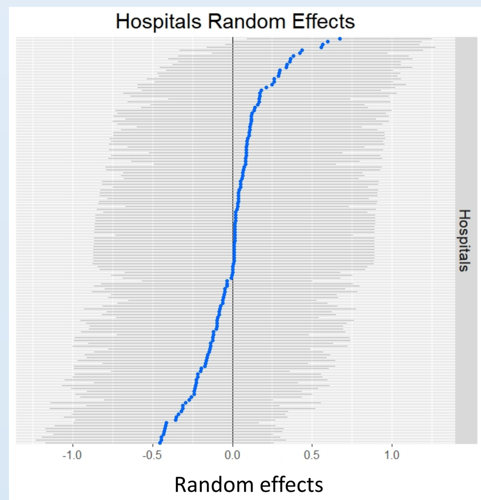

Fig. 4.

Furthermore, as the main goal of our research, we want to investigate the **quality of the hospitals**.

FRAGILITY (random intercept)	$-\hat{\sigma}$	0 (mean)	$+\hat{\sigma}$
GRADE 1 2 3	0.94	0.97	0.95
GRADE 4	0.74	0.82	0.71
GRADE 5	0.47	0.61	0.71
GRADE 6	0.26	0.30	0.38

Fig. 5.

We interpret the survival rates using our fragility index (grade). First, we classify hospitals based on the distance from the mean (0) of their random intercept. Then we compute the average of the survival rates grouping by the hospitals whose intercept is one standard deviation away from the mean and by the fragility of patients based on our index.

As we can observe from Fig. 5, the survival rates decrease with increasing grade. For easy tasks (grade 1 2 3) all the hospitals behave in the same way, but the **difference pops up when the task become harder**. For example, rank 5 patients going to a positive effect hospital increase their survival rates up to 20 percentage points!

After highlighting the differences in hospitals' quality, the management office must investigate further the reasons why. Is it due to a need of better preparation of the doctors? Cleaner rooms? Less overcrowding?

SUPPORT TO DOCTORS – LOGISTIC REGRESSION FOR REHOSPITALIZATION

Then we move our attention to a deeper stage. After having investigated the effects of the hospitals over three years, we focus on the single hospitalization to help doctors making their decisions.
In particular, taking into account only the information available up to the first hospitalizations, we create a logistic regression model to predict if a patient will be re-hospitalized within 500 days. We have 6500 patients in 134 hospitals.

Logistic Linear Mixed Effects Model

$$logit(y_{ij}) = \beta_0 + \beta_1 * log(age_{ij}) + \beta_2 * log(duration\ of\ hosp_{ij}) + \beta_3 * level\ of\ risk_{ij} + \beta_4 * n°\ comorb_{ij} + \alpha_j$$

$$\boldsymbol{\alpha} \sim N(0, \sigma_b^2)$$

y_{ij}: rehospitalization indicator (1 rehospitalized) for patient i in hospital j
$level\ of\ risk$ instead of the entire grade since we have only one hospitalization
$comorbidities$ such as pulmonary problems, arrhythmia, diabetes…
α_j: random intercept due to hospital j visited by patient i

How can this model help doctors? Consider this possible **real life example:**
A doctor suggested a prognosis of 50 days for a patient. At the end of this period, our model comes into the picture and predicts if it will be needed a future hospitalization. Associated with output 0 there won't be a future hospitalization so it will likely be safe for the patient to go home. Otherwise, the patient will need further attention and the doctor will have to decide whether to send him home with an eventual prescription and a future check or to extend the current hospitalization.

Classification features of the model
AUC: 0.64, Specificity: 0.53, Sensitivity: 0.67
In this case we prefer sensitivity since it is more important to understand if the patient needs further treatments. Our model does not perform well, we have few information since we consider only one hospitalization and the model cannot capture what is really happening. Moreover it is not trivial, especially from doctor's side, to give a specific and correct diagnosis. Fragility is difficult to capture and patients arrive at hospitals with disparate stages of the disease.

NESTED MIXED EFFECTS LINEAR MODEL- DURATION OF A HOSPITALIZATION

Finally, we study the duration of a generic hospitalization with a mixed effects linear model, therefore we use a single hospitalization as a statistical unit. We have 1958 hospitalizations of 1000 patients in 123 hospitals.
This model can be a support to the previous one, as the doctor can predict the duration of the first hospitalization and start the treatment or it might be an helpful organization tool, for example, to reserve rooms.

Linear Nested Mixed Effects Model with heteroscedastic residuals

$$log(y_{ijk}) = \beta_0 + \beta_1 * log(age_{ijk}) + \beta_2 * log(cumulative\ time_{ijk}) + \beta_3 * grade_{ijk} + \beta_4 * n°\ comorb_{ijk} + \alpha_k + \gamma_{jk} + \varepsilon_{ijk}$$

$$\boldsymbol{\alpha} \sim N(0, \sigma_{hosp}^2) \qquad \boldsymbol{\gamma} \sim N(0, \sigma_{pat}^2) \qquad \boldsymbol{\varepsilon} \sim N(0, \sigma_{eps}^2)$$

y_{ijk}: duration of hospitalization i for patient j in hospital k
$cumulative\ time$: time since the first hospitalization
α_k: random intercept due to hospital k
γ_{jk}: random intercept due to patient j in hospital k

We consider a **nested random effect** because the effect of the hospital is in common for all its patients, who have one or more hospitalizations in the same hospital. To enrich the model, we consider **heteroscedasticity of residuals**, since we observe a different variability over time: patients follow treatment paths that lead to a subjective disease evolution.
We group by total time spent in hospital to then make a plot of the residuals (Fig. 6), the red dots are closer to the center, while the blue ones are spread more widely.

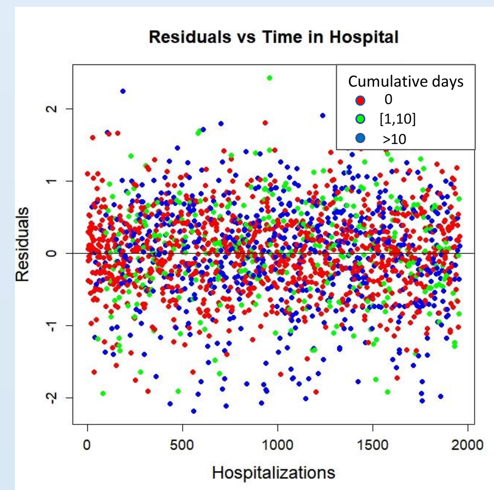

Fig. 6.

Analysis of the random effect
We expect a greater portion of variance explained by the patient's level, because there are more differences between two patients rather than two hospitals. We underline this fact from PVRE indexes:

$$PVRE_{pat} = \frac{\sigma_{pat}^2}{\sigma_{pat}^2 + \sigma_{osp}^2 + \sigma_{eps}^2} = 0.21 \qquad PVRE_{hosp} = \frac{\sigma_{hosp}^2}{\sigma_{pat}^2 + \sigma_{osp}^2 + \sigma_{eps}^2} = 0.06$$

A mixed effects model yields a variance associated with each random factor and the residual variance, so its not entirely clear which to use when calculating the R2. To solve this problem two type of R2 have been defined [5]:

$$\text{marginal } R2 \cong \frac{\sigma_{fixed}^2}{total\ variance} \cong 0.184 \qquad \text{conditional } R2 \cong \frac{\sigma_{fixed}^2 + \sigma_{random}^2}{total\ variance} \cong 0.300$$

The model can't capture enough variability for us to entrust it, because we don't have information on the evolution of the patients' diseases and there is too much medical complexity that our data cannot explain. Anyway, doctors can use this model to compare their decisions.

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