Group 23

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1. What is the general domain/subject area of this project?

This project will focus on the area of cardiovascular disease (CVD). In this study, we aim to study the association between serum biomarkers and mortality rates among patients with diagnosed heart failure.

2. What data will you use, and what is the source?

This project will be based on medical records of 299 patients of heart failure, with left ventricular systolic dysfunction. The dataset was collected and analyzed by Ahmad et al (*PLoS One*. 2017;12(7):e0181001.). Then in January 2020, the dataset was elaborated and donated to the University of California Irvine (UCI) Machine Learning Repository by Davide Chicco under the same Attribution 4.0 International (CC BY 4.0) copyright *(BMC Med Informatics Decis Mak 2020 201*. 2020;20(1):1-16). We downloaded this dataset from the UCI Machine Learning Repository.

The dataset can be accessed through

<https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+records>.

3. What primary questions will you seek to answer?

The association between serum creatine, a biomarker indicating renal dysfunction, and mortality rates for patients with heart failure.

4. What secondary questions will you seek to answer

* The association between serum creatine and death risks 30 days after beginning follow-up among patients with heart failure.
* Also, we will explore whether and how demographical features and health conditions modify the association between serum creatine and mortality rates/Death 30-day in the patients with heart failure.

5. What outcome(s)/endpoint(s) will you use?

* The primary outcome in this study is the survival time of the patients.
* The secondary outcome is the death (0 for alive patient, and 1 for dead patient) 30 days after beginning follow-up of the patients. It is a binary outcome.

6. Statistical Analysis Plan

1. Data cleaning: although the dataset has been elaborated by Davide Chicco, we will check any potential missing data in the outcome, exposure, and covariates. We will report the number of missing data and if the number is less than 10%, we will consider including a “missing” indicator for categorical variables and imputing continuous variables. We will report the final number of patients included in our study.
2. Checking the exposure:

The primary exposure, serum creatine, which is continuous, is usually categorized into two different levels (≤ 1.5 mg/dL for the normal level vs, and > 1.5 mg/dL for the abnormal level). In this project, we will first treat the serum creatine as a continuous variable and calculate its sample mean, standard deviation, median, and range. Then we will treat it as a binary variable and calculate the proportion of normal and abnormal levels in patients.

1. Checking the outcomes:

We will calculate the average person-time until death in the normal serum creatinine group and the abnormal serum creatinine group. We will also calculate the Death 30-day in these two groups. Survival plots will be made to visualize the mortality rates in serum creatinine groups. Chis-squared tests will be applied to test the difference of Death 30-day in these groups.

1. Checking other covariates.

In this project, age (continuous), sex (male vs. female), anemia (yes vs. no), diabetes (yes vs. no), ejection fraction (≤ 30, 31-44, and ≥ 45), smoking (yes vs. no), platelets (continuous, kilo platelets/mL), and serum sodium (continuous, mEq/L) will be considered as covariates.

The proportions for categorical covariates and mean (standard deviations) for continuous covariates in normal serum creatinine group and abnormal serum creatinine group will be calculated and compared using chi-squared tests and t-tests respectively.

1. Modeling analysis

First, we will do a crude model to assess the association between serum creatine (normal vs. abnormal) and mortality rates using a Cox proportional-hazards model. The outcome is the survival time with the event (0 for censored and 1 for death) and the only predictor is serum creatine (normal vs. abnormal). Second, based on the crude model we will adjust for age, sex, anemia, diabetes, ejection fraction. Last, we will further adjust for other serum biomarkers including serum sodium and platelets value to get a fully adjusted model.

For Death 30-day, logistic regressions models will be applied following the same adjustment procedure mentioned above from the crude model to the fully adjusted model.

To check whether the findings from models using categorical serum creatinine are robust, we replace the exposure with continuous serum creatinine value for all the models mentioned above.

1. Subgroup analysis for potential effect modification.

To check whether effect modification exists, we will include an interaction term between serum creatine (normal vs. abnormal) and age (<65 vs. ≥65), sex, diabetes, anemia, ejection fraction, smoking, platelets, and serum in turns into the model. The p-value of the interaction term will be used to determine if there are any effects modifications. The same process will be applied for continuous serum creatine values.

1. Checking nonlinearity

To check whether the relationship between serum creatine and mortality risks is linear, we will replace the linear term in the fully adjusted model with a natural spline of serum creatine. The knots and degrees of freedom of the spline will be determined during the following analysis.

7. What are the biggest challenges you foresee in answering your proposed questions and completing this project.

We foresee the biggest problem may be the violation to the proportional-hazards assumption. Also, we are concerned that the limited sample size may prohibit us from including such a number of prediators in the model.

8. Will you seek domain expertise? Why or why not? If so, from whom?

Yes. Because this project is very closely linked to clinical medicine especially CVD and renal diseases, we need to discuss with experts in this area. However, given the limited time of this project and the limited resources, we would like to read related articles and to learn background knowledge first. Then, we will put unresolved questions into the discussion board on Canvas to see if any classmates can help us. We believe our class incorporates students from different disciplines related to human health. There must be somebody who can help us.

9. What software package(s) will you use to complete this project?

* R 4.1.1 (R core team) will be used to manipulate data and to do model analysis
* Tidyverse package will be used to make out work easier.
* Survival package will be used to conduct Cox proportional-hazard models.
* ggfortify and gglot2 will be used to visualize our results.