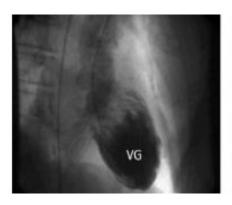
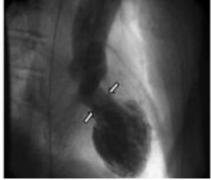
Takotsubo Syndrome: Prediction of hospitalization outcomes

Python Machine Learning Project
July 10th 2021





Daisuke KUWABARA Nesrine BENANTEUR

OUTLINE

Introduction: Reminders of basic heart physiology to understand the context

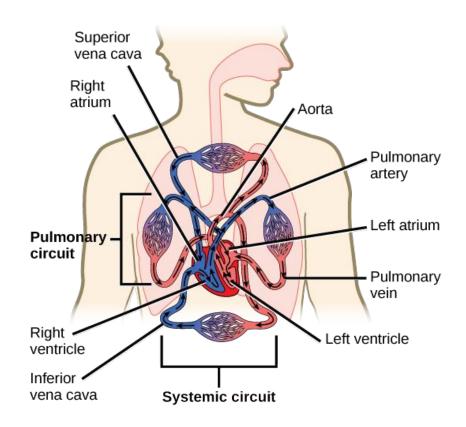
Takotsubo Syndrome

Description of the cohorts and the variables used for prediction

Algorithms predictions

Conclusion: Perspectives and improvements

GENERAL HEART PHYISOLOGY TO UNDERSTAND THE CONTEXT

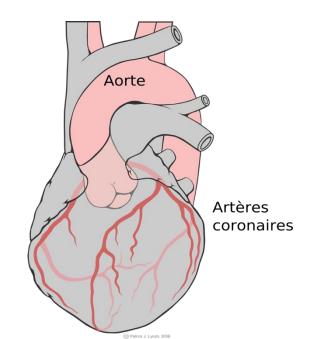


The heart is made of specialized cardiac muscle tissue called **myocardium**.

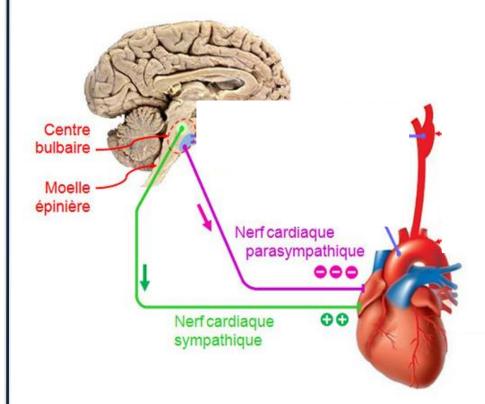
It is made of specific cells called cardiomyocytes.

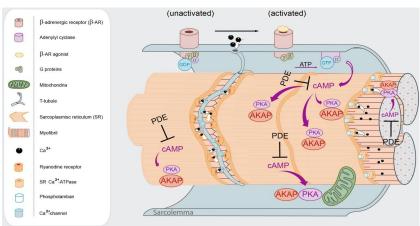
Circulatory system: network consisting of blood, blood vessels, and the heart.

This network supplies tissues in the body with oxygen and other nutrients, transports hormones, and removes unnecessary waste products.



GENERAL HEART PHYISOLOGY TO UNDERSTAND THE CONTEXT



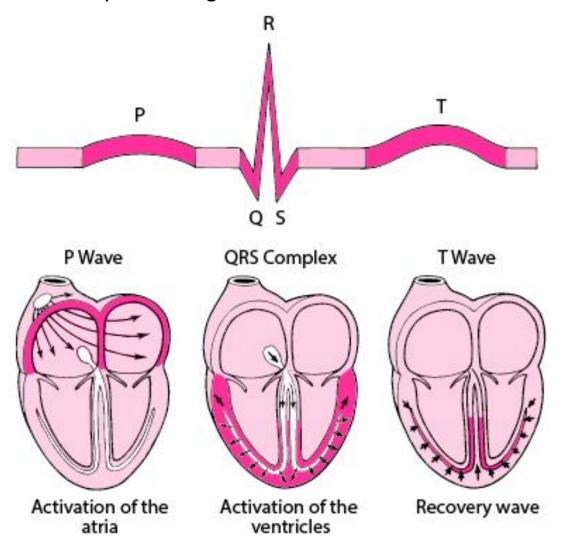


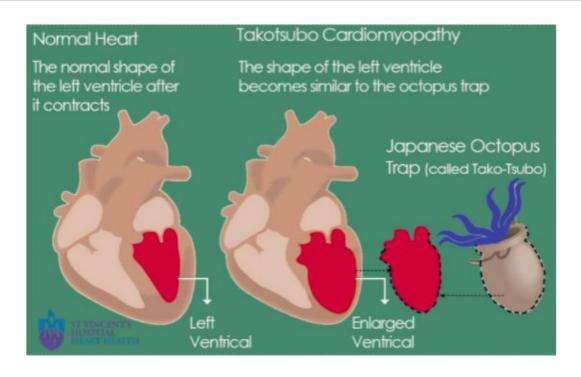
How does the heart beat?

- Nerve conduction: sympathic cardiac nerve (increases the heartbeat) or parasympathic cardiac nerve (decreases the heartbeat).
- Biochemicals: catecholamines (adrenaline, noradrenaline) are released to increases the contraction of the cardiomyocytes.

GENERAL HEART PHYISOLOGY TO UNDERSTAND THE CONTEXT

▶ The heart rate can be analyzed through an exam called ECG.

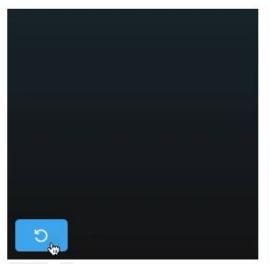


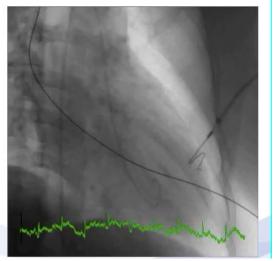


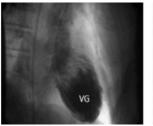
Takotsubo cardiomyopathy is a transient weakening of the left ventricle, the heart's main pumping chamber.
Usually: result of severe

emotional or physical

stress.

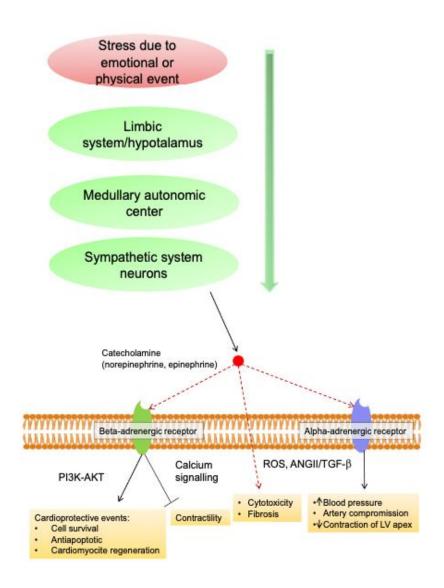








Possible causes:



Lots of hypothesis today, but articles seem to all incriminate a catecholamine toxicity.

High prevalence in middle-aged women seem to show that estrogen Deficiency due to menopause might predispose them to the disease.

What happens during a Takotsubo event?

Left ventricle pumps
blood less efficiently

Amount of blood going out
of the heart decreases
significantly (LVEF >)

Organs receive less blood
and suffer from the lack of
oxygen and nutrients.

Why chest pains?

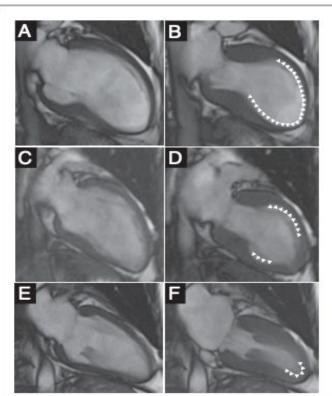
- Coronary arteries receive a lot less blood than usual.
- → Cardiomyocytes aren't fed in oxygen and nutrients, and die.

Consequences?

- Cardiogenic shock: the blood pumped into the whole body cannot meet the other organs' needs, provoking damages to the liver, kidneys from lack of oxygen, which can be permanent.
- Rhythmic abnormalities
- Thrombus due to residual blood in the left ventricle.
- Death

<u>Criterion for Takotsubo diagnosis:</u> (Mayo Clinic, 2004)

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.



A, C, E: Diastole – heart relaxing and filling up with blood.

B, D, F: Systole – heart contraction

Diversity of left ventricle contraction patterns

<u>Criterion for Takotsubo diagnosis:</u> (Mayo Clinic, 2004)

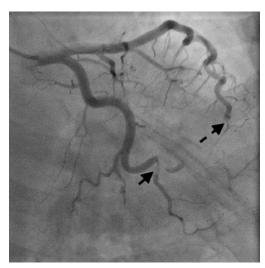
- 1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
- 2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.



Normal coronary arteries on the left side of the heart



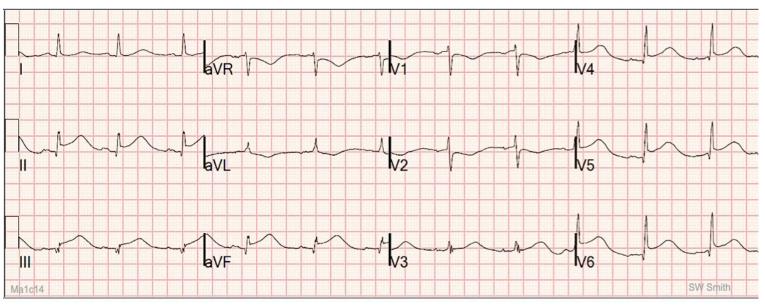
Normal coronary arteries on the right side of the heart

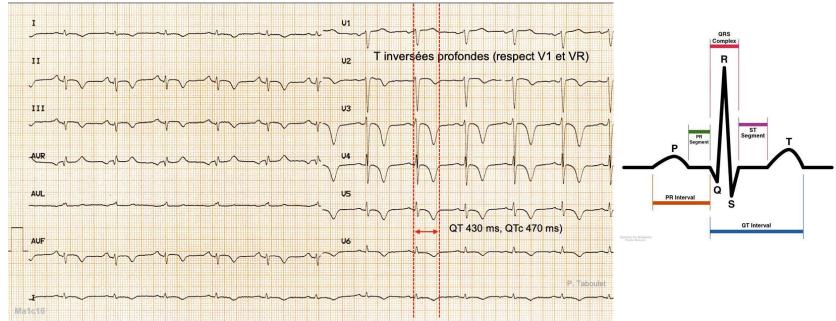


Coronary arteries obstructed

<u>Criterion for Takotsubo diagnosis:</u> (Mayo Clinic, 2004)

- 1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
- 2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- 3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.





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- 2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- 3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
- 4. Absence of: a. Pheochromocytoma



b. Myocarditis



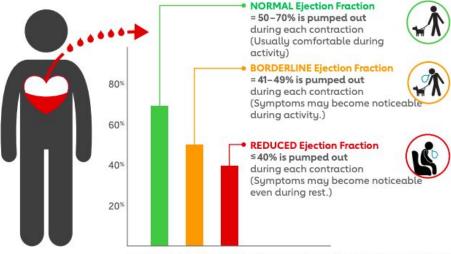
TAKOTSUBO SYNDROME: PROBLEMATIC

Project goals:

- Predict the in-hospital complications
- Predict the kind of heart failure to anticipate the medical care needed.



How much blood is pumped out?



It is also possible to have a diagnosis of heart failure with a seemingly normal (or preserved) ejection fraction of greater than or equal to 50%.

Who?

Takotsubo patients between 2015 and 2021 from the CHU de Toulouse.

What?

Variables selected by reading research articles on the short and long-term prognosis or diagnosis of the disease.

How?

Reading the patients records and extracting the data patient by patient.

	âge	Date hospit init		lomme	▼ poids	▼ tai	lle ▼	IMC (kg/ ci = ATCD dépression/ =	ATCD psychiatrique	patho neurologiques	*	HTA 🔻	Dyslipidém =	Tabac 🔻	Diabète =	IRC	AVC/AIT	ATCD Canc ▼	Cance
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30/6/1940		1 10/	2/2016		0	50	1,53	21,36)	0	0	1	0	0	1		0 0	0	
20/10/1962		8 25/	2/2016		1	60	1,78	18,94)	0	1	0	0	1	0		0 0	0	
19/8/1939		1 1/	3/2016		0	70	1,56	28,76)	0	0	1	0	0	0		0 0	1	
6/11/1929		1 28/	2/2016		0	57	1,54	24,03)	0	1	1	0	0	0		0 0	0	
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20/4/1944	7	7 20/	4/2016		0	80	1,56	32,87)	0	1	1	0	0	1	1	0 1	1	9
29/5/1991		0 24/	4/2016		0	63	1,58	25,24)	0	0	0	0	0	0		0 0	0	
3/9/1958		2 2/	5/2016		1	55	1,68	19,49)	1	0	0	1	1	1		0 0	0	
11/5/1928		3 18/	5/2016		0	55	1,55	22,89)	0	0	0	0	1	0		0 0	0	
12/3/1949		2 2/	6/2016		0	80	1,55	33,30)	0	0	1	1	0	0		0 0	0	
11/8/1939		1 3/	6/2016	,	0	98	1,69	34,31)	0	0	1	1	1	1		0 0	0	
12/10/1934		6 13/	7/2016		0	67	1,7	23,18)	0	1	1	0	0	0		0 1	1	
27/6/1949	7	2 23/	7/2016		0	65	1,69	22,76		0	0	1	0	0	0		0 0	0	
12/3/1931		0 23/	7/2016		1	73	1,7	25,26)	0	0	0	0	0	0		0 0	0	7
27/7/1955		5 26/	7/2016		0	82	1,67	29,40		0	0	1	0	1	0		0 0	0	
30/7/1955		5 17/	8/2016		0	58	1,63	21,83)	0	0	1	0	1	1	8	0 0	0	9
26/5/1933		8 20/	9/2016		0	57	1,55	23,73)	0	0	1	0	0	1		0 0	0	
31/12/1941		9 27/	9/2016		0	74	1,5	32,89)	0	0	1	1	0	0		0 0	0	
27/6/1952		9 5/1	0/2016		0	58	1,6	22,66		0	0	1	0	0	0		0 0	0	
1/7/1935		6 12/1	0/2016		0	60	1,58	24,03		0	0	1	1	0	0		0 0	0	
19/1/1944		7 19/1	0/2016		0	55	1,55	22,89)	0	0	1	1	0	0		0 0	0	
20/2/1943		8 13/1	1/2016		0	70	1,76	22,60)	0	0	0	0	0	1		0 0	0	7
31/1/1939		2 29/1	1/2016		0	68	1,64	25,28		0	1	1	0	0	0		0 1	0	
15/1/1949		2 28/1	2/2016		1	70	1,73	23,39		0	0	0	0	1	0		0 0	0	
27/12/1944		6 4/	1/2017		0	49	1,6	19,14)	0	0	0	0	1	0		0 0	0	
3/10/1942		8 20/	1/2017		0	60	1,54	25,30		0	0	0	0	0	0		0 1	0	
3/5/1973	4	8 26/	1/2017		1	84	1,86	24,28)	0	0	0	0	0	0		0 0	0	
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5/12/1946	- 1	4 8/	2/2017		0	75	1,58	30,04)	0	0	1	1	0	0		0 0	1	
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16/2/1949		2 27/	2/2017		0	67	1,59	26,50)	0	0	0	1	1	0		0 0	1	
31/12/1949		1 14/	5/2017		0	64	1,69	22,41)	0	1	0	1	1	0	4	0 0	0	9
11/6/1959	(2 11/	6/2017		0	65	1,68	23,03		0	0	0	1	0	0		0 0	0	
19/4/1924		7 14/	6/2017		0	53	1,6	20,70)	0	0	_r_ 1	0	0	0		0 0	0	
8/2/1930		1 20/	6/2017		0	60	1,57	24,34)	0	0	0	0	0	0		0 0	1	
20/10/1043			6/2017		^	E7	16	22.27		n	4	0	0	^	0	1	0 1	^	$\overline{}$

DEMOGRAPHICS

Age, BMI, Sex.

MEDICAL HISTORY

- Depression or Anxiety
- Psychiatric disorders
- Neurological diseases
- Hypertension
- Dyslipidemia
- Smoking
- Diabetes
- Chronic Renal Failure
- Stroke or Transient Ischemic Attack (TIA)
- Cancer history or active Cancer
- Chronic Obstructive Pulmonary Disease (COPD) or asthma
- Alcoholism
- Cardiac diseases history

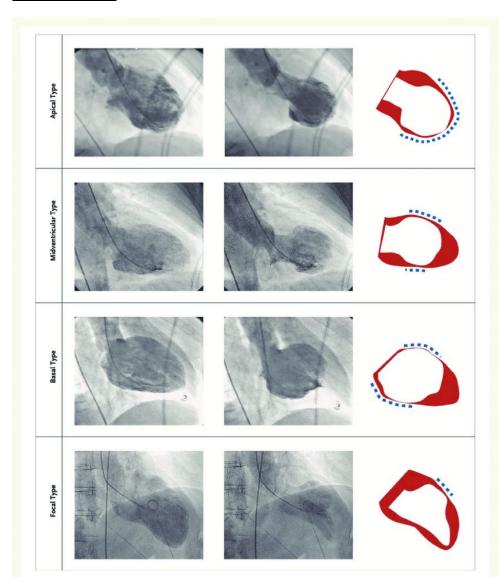
STRESS FACTOR

- Emotional
- Physical

TREATMENTS BEFORE/AFTER EVENT

- Beta Blockers
- Angiotensin Converting Enzyme Inhibitor
- Angiotensin II receptor blockers
- Aspirin
- Antiplatelets drugs
- Oral anticoagulation drugs
- Statins
- Anti-depressants and anxiolytics

ANATOMY



Apical type

Medioventricular type

Basal type

Focal type

HAEMODYNAMICS

- Left Ventricle Ejection Fraction (LVEF)
 - entry LVEF
 - out LVEF (to predict)
- ECG abnormalities (ST +, long QT, T-)

BIOMARKERS

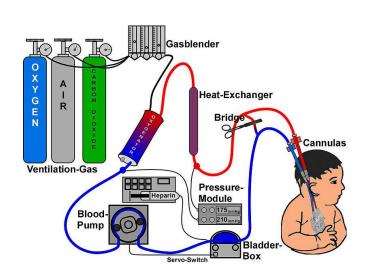
- Troponin T (entry and peak)
- NT pro-BNP
- CRP

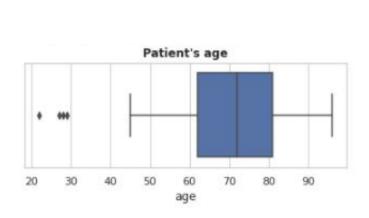
CORONAROGRAPHY

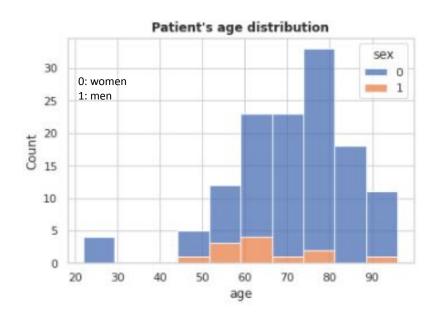
- Harm
- Healthy

IN-HOSPITAL COMPLICATIONS (to predict)

- Heart Failure
- Right Ventricle Harm
- Ventricular arrhythmia
- Left ventricle thrombus
- Cardiogenic shock
- ECMO (Extracorporeal membrane oxygenation)
- Death



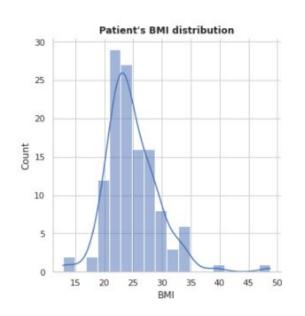


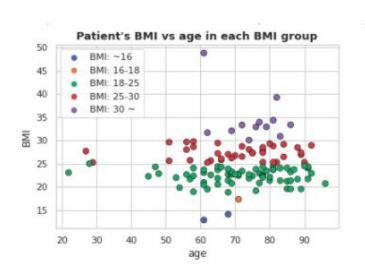


Here above you can see our cohort's age distribution. Most of our patients are women, and the average age is around 71 years old.

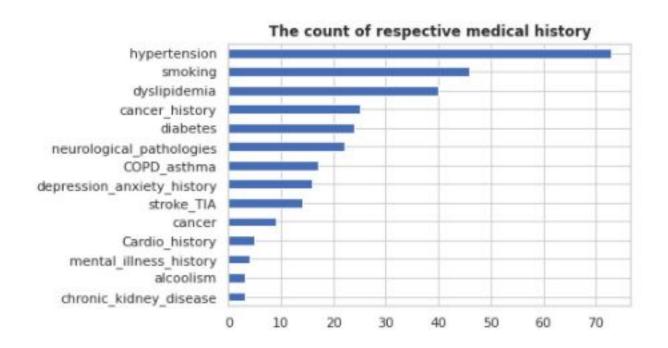
BMI Category

Value	Category	Groups		
~ 16	denutrition	1		
16-18	underweight	2		
18-25	normal	3		
25-30	overweight	4		
30 ~	obesity	5		





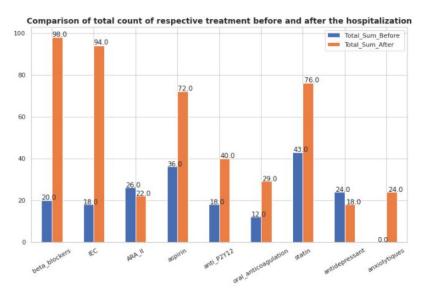
Here above you can see our cohort's BMI distribution. Most of our patients have a normal BMI.



Here above you can see our cohort's medical history.

Most of our patients have a history of hypertension and smoking.

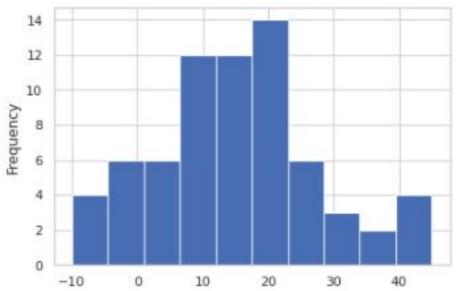
We can also find history of dyslipidemia, cancer, diabetes, neurological pathologies (mostly degenerative diseases), COPD or asthma, depression or anxiety, stroke or TIA, mental illnesses (excluding depression and anxiety), alcoholism, chronic kidney disease, cardiovascular disease and alcoholism.



Here above you can find our cohort's treatments, before and after the Takotsubo event.

- As you can see, there a significant rise in the prescription of cardioprotective molecules like beta blockers, Angiotensin Converting Enzyme Inhibitor which lower the heartbeat and the blood pressure, respectively. We wan see the same tendency with treatments like aspirin, anti P2Y12, and oral anti-coagulation drugs which prevents blood clots, a very prevalent complication found in Takotsubo patients.
- The slight drop Angiotensin II receptor blockers might be explained by the rise in the use of Angiotensin Converting Enzyme Inhibitor, which basically has the same effect as Angiotensin II receptor blockers.
- The rise in the prescription of statins might be due to the discovery of coronary disease in patients on which we performed a coronarography.
- The slight drop in antidepressant prescription and rise in anxiolytics might be due to an adjustment In treatments: indeed, the effect of new anti-depressant takes week to be observable, while anxiolytics have an immediate effect.



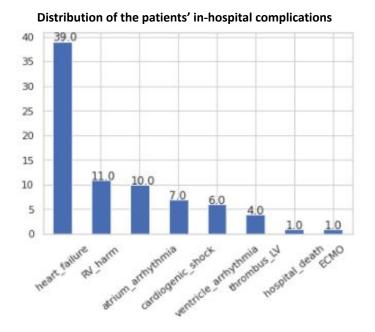


Here above you can find our cohort's LVEF evolution's distribution.

The x axis represents the difference between the LVEF after and before hospitalization (in percentage).

As you can see, most of our patients can see their LVEF increasing after their stay at the hospital.

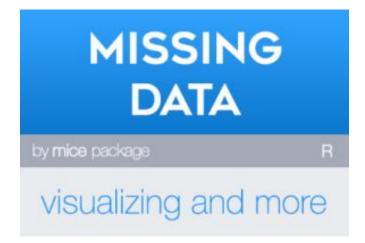
The negative part represents the proportion of patients for which the LVEF decreased after hospitalization. This might be a sign of severe heart failure, and the patients are usually followed up very seriously after hospitalization.



Here above you can find our cohort's in-hospital complications distribution.

Heart failure is the most prevalent complication here, while extreme treatment like the use of ECMO, or death are less likely to happen, which is the tendency observed in other cohorts studied in different publications.

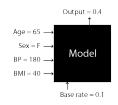
ALGORITHM PREDICTION



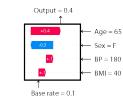












MICE (Multivariate Imputation by chained equations)

Multiple Imputation by Chained Equations is a robust, informative method of dealing with missing data in datasets. The procedure "fils in" missing data through an iterative series of predictive models.

Data Leakage:

MICE is particularly useful if missing values are associated with the target variable in a way that introduces leakage. For instance, let's say you wanted to model customer retention at the time of sign up. A certain variable is collected at sign up or 1 month after sign up. The absence of that variable is a data leak, since it tells you that the customer did not retain for 1 month.

Confidence Intervals:

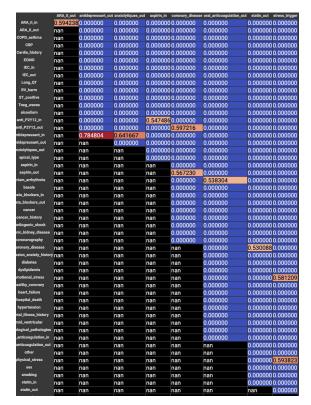
MICE can be used to impute missing values, however it is important to keep in mind that these imputed values are a prediction. Creating multiple datasets with different imputed values allows you to do two types of inference:

- Imputed Value Distribution: A profile can be built for each imputed value, allowing you to make statements about the likely distribution of that value.
- Model Prediction Distribution: With multiple datasets, you can build multiple models and create a distribution
 of predictions for each sample. Those samples with imputed values which were not able to be imputed with
 much confidence would have a larger variance in their predictions.

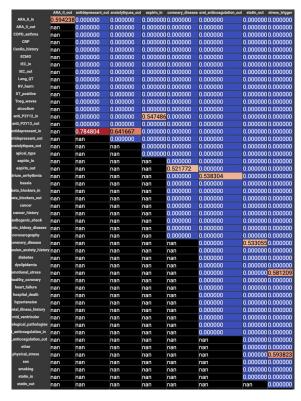


Checking correlation before and after imputation gives an insight of how imputation changes the each distribution of variable and how these variables correlates to each other.

Correlation Before Imputation



Correlation After Imputation



Continuous variables

Binary

variables



Observation

We can observe there is no significant difference of correlation before and after imputation *Note that anti_P2Y12_out and coronary_disease has no correlation after imputation, which is simply because this correlation has its threshold 0.5 and the correlation become slightly lower than that.

Heart Failure:

- Target
 - Heart Failure
- Strategy
 - Binary Classification
- Algorithm
 - PyCaret(AutoML)
 - LightGBM with Optuna
 - <u>LightGBM</u> is a gradient boosting framework that uses tree based learning algorithms. It is designed to be distributed and efficient with speed, memory usage, accuracy, parallel computing, large-scale data[1].
 - Optuna is an automatic hyperparameter optimization software framework, particularly designed for machine learning[2].
- Evaluation Metrics:
 - Accuracy
 - Precision
 - The fraction of relevant instances among the retrieved instances
 - Recall
 - The fraction of relevant instances that were retrieved
 - AUC
 - SHAP: Explainability of the model
 - SHAP(SHapley Additive exPlanations) is a game theoretic approach to explain the output of any machine learning model. It connects optimal credit allocation with local explanations using the classic Shapley values from game theory and their related extensions.
 - 1. https://lightgbm.readthedocs.io/en/latest/
 - 2. https://github.com/optuna/optuna/optuna
 - 3. https://github.com/slundberg/shap

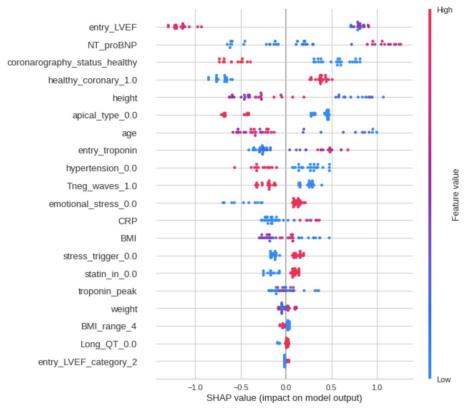
Heart Failure:

Algorithm/Metrics	Accuracy	Precision	Recall	AUC
PyCaret: Naive Bayes	75.56%	57.54%	73.33%	85.50%
PyCaret: Logistic Regression	74.44%	60.00%	39.33%	81.83%
PyCaret: Random Forest Classifier	74.44%	73.33%	19.33%	78.73%
LightGBM with Optuna	72.27%		_	

Observation

PyCaret's Naive Bayes shows the highest Recall rate, which is the main evaluation in this context. High recall shows less False Negative, that is to say, the algorithm wrongly diagnose a patient not as Heart Failure.

SHAP Value:



This plot shows the largest contribution to the model is entry_LVEF. Blue dots shows the low value of that variable while red shows the high value, which means entry_LVEF has a negative correlation with the output of heart failure.

NT_proBNP has the second largest contribution to whether patients have Heart Failure or not.

Coronarography's healthy status comes as third factor. It shows unhealthy coronarography status tends to lead to Heart Failure



This plot shows each variable contribution for an individual patient. We can observe the same tendency as above plot.

Inhospital Complications:

- Target
 - Inhospital Compilications (Heart Failure, RV harm, Atrium Arrhythmia, Cardiogenic Shock, Ventricle Arrhythmia, Thrombus LV, Hospital Death, ECMO)
- Strategy
 - Multi-Label Classification
- Algorithm
 - Decision Tree Classifier
 - Multilabel K Nearest Neighbours
 - Multilabel K Nearest Neighbours with Grid Search
- Evaluation Metrics:
 - Exact Match Ratio(EMR)
 - The Exact Match Ration extends the concept the accuracy from the single-label classification problem to a multi-label classification problem
 - One of the drawbacks of using EMR is it does not account for partially correct labels
 - Hamming Loss
 - Hamming Loss computes the proportion of incorrectly predicted labels to the total number of labels
 - For a multi-label classification, we compute the number of False Positive and False Negative per instance and average them over the total number of training instances

Inhospital Complications:

Algorithm/Metrics	Exact Match Ratio(EMR)	Hamming Loss		
Decision Tree Classifier	46.15%	10.26%		
Multilabel K Nearest Neighbours	48.72%	8.97%		
Multilabel K Nearest Neighbours with Grid Search(k:22, s:0.5)	61.54%	7.37%		

Observation

Decision Tree and KNN(K Nearest Neighbours) shows nearly same result at the beginning. With grid search, KNN improves its performance by more than 10% for EMR and less than 1% for Hamming Loss

Implementation of Multi KNN with Grid Search

CONLUSION AND PERSPECTIVES

- Difficulty of data collection: precision.
- Clinical features mostly how about genetics, epigenetics, proteomics...?
- Difficulty in data processing: dropping data when we already have just a few?
- Make the algorithm more precise by distinguishing the physical/emotional stresses.
- Contradiction of adopting the latest technologies.

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