Identifying most responsive patients to a fibrinogen injection: a prescriptive approach to treat traumatic hemorrhagic schocks

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Context and problem statement

Fibrinogen is a widely used molecule to treat patients suffering from a traumatic hemorrhagic shock (HS); indeed, it is the precursor of fibrin paramount for the constitution of a robust clot. However, despite this strong physiological rationale there is a lack of scientific evidence of its positive impact on all-cause mortality. This project builds on a previous study who concluded that 'fibrinogen administration within the first 6 hours of a traumatic hemorrhagic shock did not decrease all-cause day-one mortality'. We aim at identifying a most responsive sub-population to fibrinogen injection.

The data at at a glance

1027 patients, 22 variables selected by a panel of experts

Row	CPA	...	Fibrinogen	DC	Treatment
1	0	...	1.5	1	1
2	1	...	0.9	0	0

Table 1: Data points examples

Variable	CPA	...	Fibrinogen	DC	Treatment
Mean	0.24		1.43	0.42	0.74
Std	NA		0.73	NA	NA

Table 2: Summary statistics

Average Treatment Effect

The average treatment effect (ATE) evaluates the effect of a treatment W (fibrinogen injection in our case) on an outcome Y (patient deceased or not) given some covariates X (medical measurements):

$$ATE = \mathbb{E}[Y_i(1) - Y_i(0)]$$

However, in our case, counter-factual $Y_i(1)$ and $Y_i(0)$ are unknown. The idea behind causal inference is to construct and compute unbiased estimators to infer the value of the ATE. While one might question the validity of such an approach, it is widely used in the medical community and thus a tool to communicate with doctors.
The results from the previous study are the following:

$$\boxed{ATE = -3.1\% \text{ with } 95\% \text{ CI: } [-8.3\%, 2.1\%]} \quad (1)$$

and therefore inconclusive.

Why a prescriptive approach?

Our goal is to identify a responsive sub-population to fibrinogen injection using prescription indication. Responsiveness being defined as an negative ATE, we wish to cluster our dataset in a way allowing us to compute ATE. This implies to have balanced enough clusters in size, but also diverse enough in terms of treatment and outcome.
Prescriptive trees (Julia) are implemented as an heuristic i.e. impossible to change the constraints. Thus, we leverage training hyperparameters to form the groups.

A first prescription with OptimalTrees

Prescriptive tree parameters	1	2	3	4	5
max depth	5	5	5	5	5
minbucket		10	10	60	40
treatment minbucket				10	10
prescription factor			0.8		0.8

Table 3: 5 prescriptive trees

We identified patients with # prescriptions in [0,5]

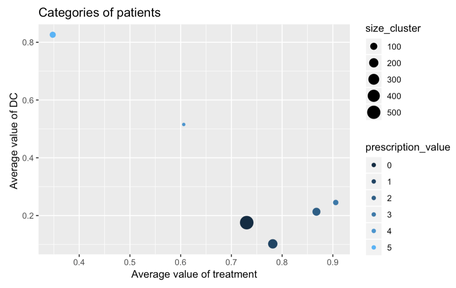

Fig. 1: Output of the 5 prescriptive trees

Robustness of categories

We study the stability of these 5 categories towards imputation and randomness in optimal trees. Thus, we make 100 imputations and train for each of these imputed datasets the 5 prescriptive trees previously described with 20 different random seeds. Therefore, we can associate to each patient a # prescription in [0,10k] and plot the distribution (**Fig. 2**). Let us look at the transition matrix for the 5 initial groups if we use this distribution and the quantiles of the initial distribution (**Fig. 3**).

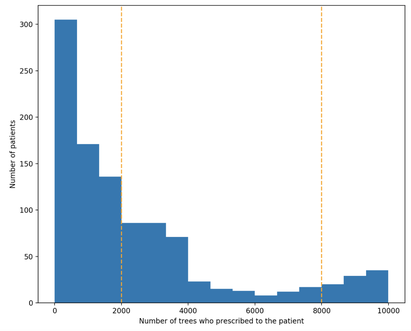

Fig. 2: Distribution of # prescription value

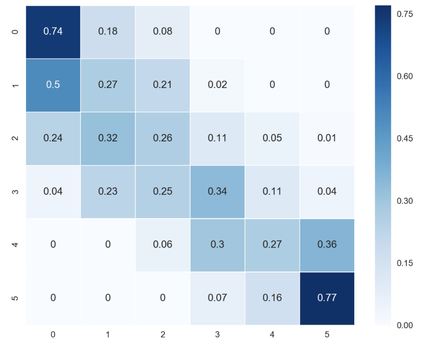

Fig. 3: Transition matrix for the 5 initial groups

Interpretability

In order to recover the interpretability lost by using 10k prescriptive trees, we trained an OCT to classify the sample in categories 0, 1 and 2 suggested by cuts on **Fig. 2**. This yield the tree **Fig. 4** with testing accuracy 84%.

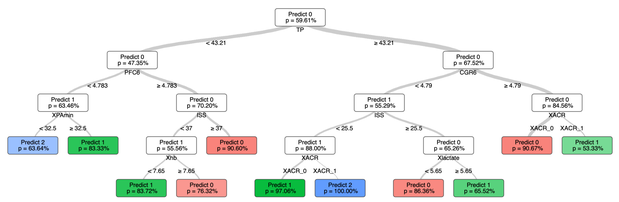

Fig. 4: Optimal Tree Classification

Formal measure of ATE

Using the same process as in (1), we computed two ATEs:

- On **group {0 + 1}**:

$$\boxed{ATE = 7.35\% \text{ with } 95\% \text{ CI: } [2.5\%, 12.2\%]} \quad (2)$$

- On **group {1 + 2}**:

$$\boxed{ATE = -16.7\% \text{ with } 95\% \text{ CI: } [-23.6\%, -9.94\%]} \quad (3)$$

These results suggest that fibrinogen injection decreases mortality for group 1 + 2 but increases it for group 0 + 1. However, these conclusions should be tempered because of:

- Survival bias: some patients die to soon to receive fibrinogen
- Prescription bias: some doctors might prescribe fibrinogen as an ineffective last resort solution

Conclusion

In this project we have used Optimal Prescriptive Trees to extract a subpopulation of patients potentially most responsive to fibrinogen injection.
While the results of the ATE seem to confirm this intuition, such a complex affirmation should be tempered.
Still, this work suggest a new way to formulate medical strategies without a clinical trial.

Future developments

- In order for this study to be directly actionable by doctors, we need to take a very close look to the temporal aspect of the variables. Indeed, for a protocol to be suggested, only variables available before the injection should be taken into account. Therefore, a key direction of development would be to repeat this study on a subset of such variables.
- Secondly, the survival bias should be addressed. One possible way would be to estimate the time of death by looking at the timeline of measurements.
- Finally, this should be replicated with synthetical data for which we know the counter-factual.