

Subgroup identification with survival decision trees:

detection of predictors associated with an early/late conversion in the successive Alzheimer's stages

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease resulting in cognitive and functional loss.

The study objective was to identify subgroups of patients converting prematurely or late from mild to moderate (or severe) dementia due to AD.

Methods

MEMORA is a prospective cohort conducted in the Resources and Research Memory Center of Lyon, France. Data include patients' etiological diagnosis, socio-demographic information, comorbidities, treatments, MMSE score and hospitalizations.

MMSE thresholds defined dementia sub-stages: mild dementia ($20 \leq \text{MMSE} \leq 26$), moderate dementia ($11 \leq \text{MMSE} \leq 19$) and severe dementia ($\text{MMSE} \leq 10$).

Data of patients between 50 and 90 y.o. with **mild dementia** due to AD seen between 2014 and 2019 were extracted.

The **censored Time To Conversion (TTC)** from mild to moderate (or severe) dementia is defined by:

1st case: the patient converted during the study period

Observed event = True

Duration = time from 1st mild dementia visit to 1st moderate (or severe) dementia visit

2nd case: the patient did not convert during the study period

Observed event = False

Duration = time from 1st mild dementia visit to last visit in the database

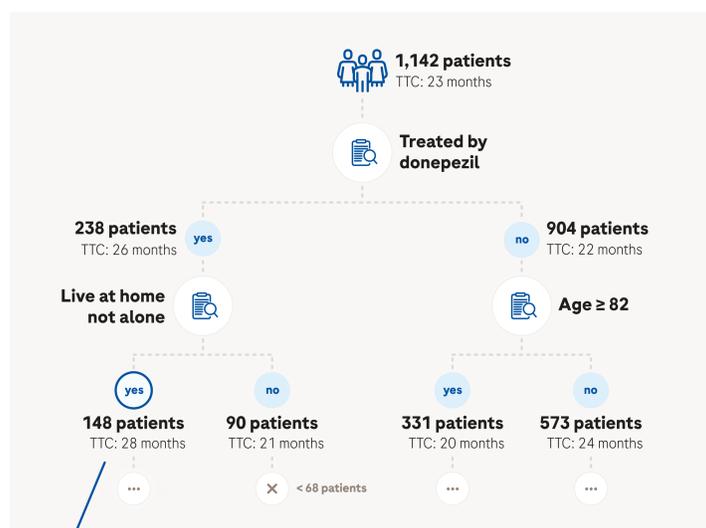
We trained **survival decision trees**, which are decision trees on which the quality of a split is measured by the log-rank splitting rule. To obtain a variety of subgroups, survival decision trees have been trained with different subsets of features.

We extracted **subgroups among the trees' nodes and leaves** with:

- at least 6% of the patients,
- no characteristic expressed via a negation,
- significantly shorter/higher TTC (assessed through Kaplan-Meier estimators) than its complementary in the cohort and than its sibling node,
- a median TTC at least 15% higher/lower than the entire cohort's,
- a median TTC further from the entire cohort than its parent node.

We plotted those subgroups in a 2D scatter plot: number of patients by median time to conversion. We kept subgroups on the widened Pareto fronts of this plot.

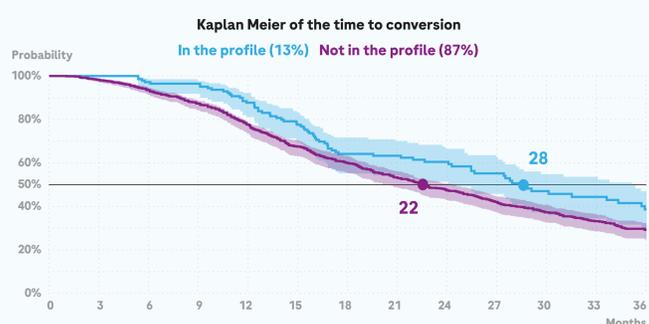
A decision tree



A late conversion subgroup

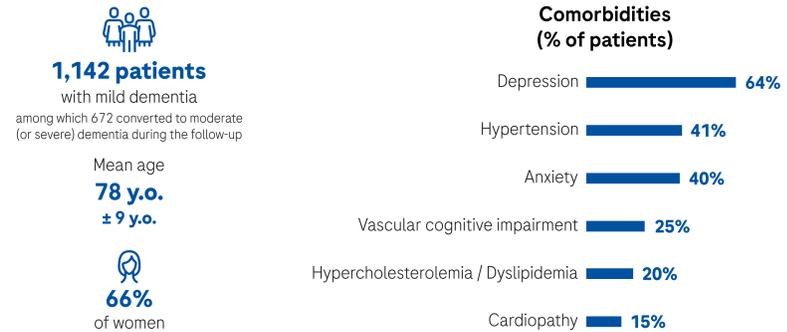
TTC = 28 months
148 patients (13%)
p-value = 0,030

- Treated by donepezil (SM* for AD)
- Live at home not alone



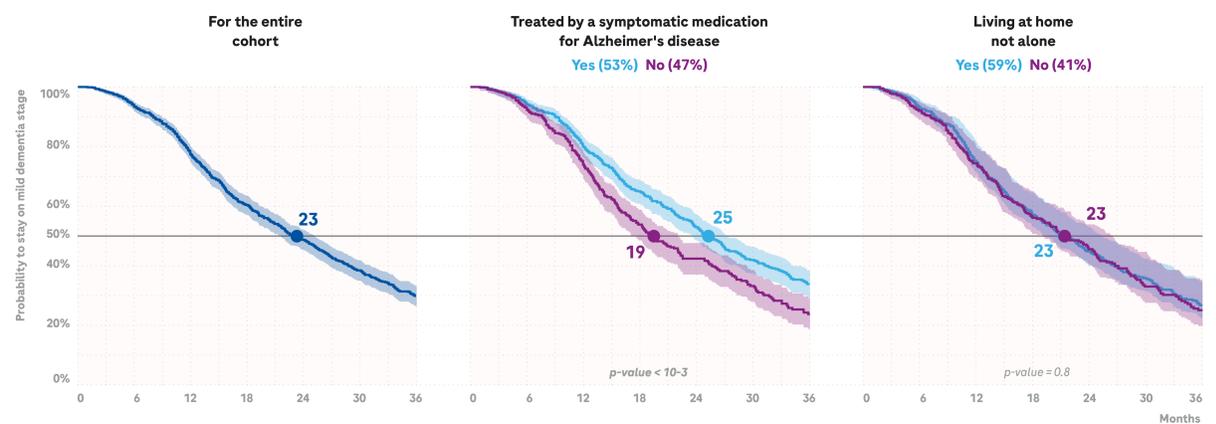
Results

Step 1: descriptive analyses



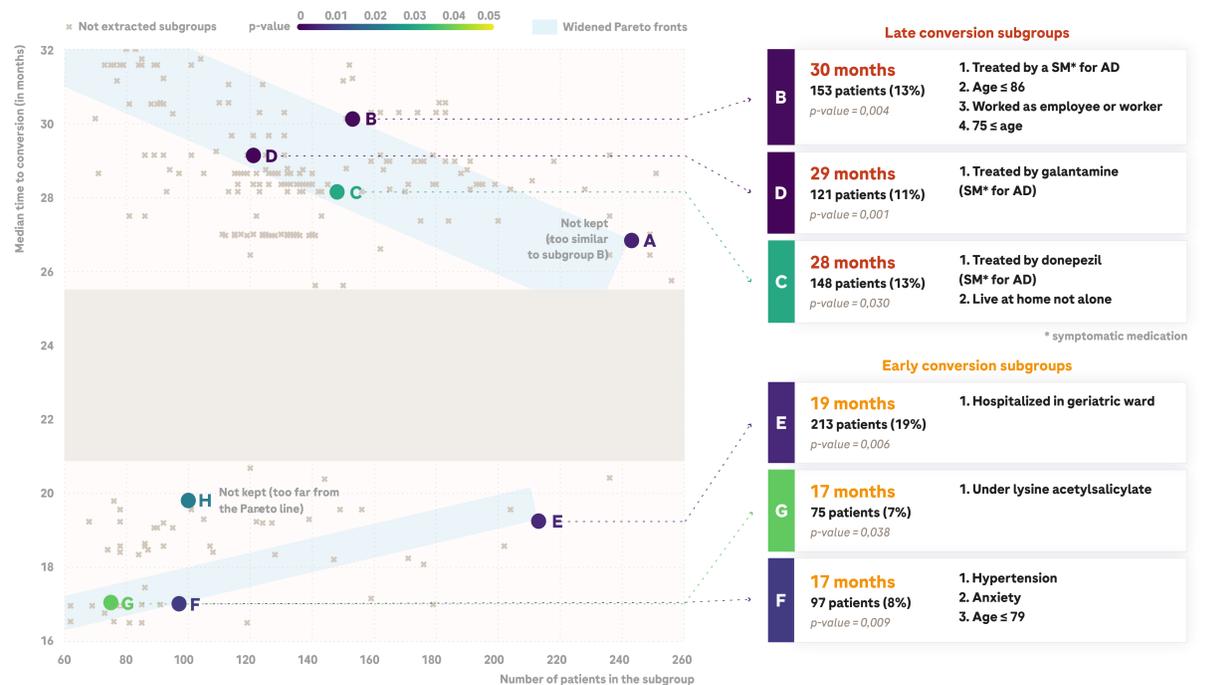
Step 2: univariate analyses

Kaplan Meier of the time to conversion from mild dementia to moderate (or severe) dementia.



Step 3: the survival trees

6 out of 338 subgroups of patients converting **early / late** from mild dementia to moderate (or severe) dementia.



Conclusion

Combining **survival decision trees** and the MEMORA database enabled the detection of patient subgroups converting earlier/late between AD stages. While the decision trees identify **combinations of features** impacting the conversion time (whereas a Cox model studies the impact of each feature one by one), the survival allowed us to model a **censored target**.

Patients treated by symptomatic medication for Alzheimer's disease are part of subgroups with a later conversion, whereas patients with hospitalization in geriatric ward or being treated by lysine acetylsalicylate converted earlier.

The variable "Living at home not alone" was not linked to later conversion (from univariate analysis), whereas when **combined with "being under donepezil treatment"** it was (from survival trees).

Glossary

AD: Alzheimer's disease
MMSE: Mini Mental State Examination
TTC: Time To Conversion

Disclosure/Fundings

ML, MP and AV are employees at HEVA.
ACI, ACH and BR are employees at ROCHE.
CM, VD and PKS are employees at Hospices Civils de Lyon (HCL).
This study was financed by Roche France and implemented by HEVA and the HCL.

