

Clinical Dataset Exploration Explanation Notebook

narrative of `clinica/clinica_data_exploration.ipynb`.

1. Objectives and Dataset

- Goal: characterize PD vs MSA (MSA-P, MSA-C) clinically; surface discriminative variables; prepare for integration with imaging models.
- Classes considered: MSA-P, MSA-C, PD (MSA-P and MSA-C are sometimes merged as MSA).

1.1 Legend

Column	Type	Short explanation
anni_dalla_diagnosi	numeric	Years elapsed since formal diagnosis.
anni_dopaminoaagonisti	numeric	Duration of dopamine-agonist therapy (years).
anni_l_dopa	numeric	Duration of levodopa therapy (years).
anno_diagnosi	numeric	Calendar year of diagnosis.
anno_esordio_disautonomia	numeric	Year of first autonomic symptom.
anno_esordio_sintomi_motori	numeric	Year of first motor symptom.
anno_esordio_sintomi_non_motori	numeric	Year of first non-motor symptom.
anno_nascita	numeric	Year of birth.
compass_gi	numeric	COMPASS-31 gastrointestinal sub-score.
compass_oh	numeric	COMPASS-31 orthostatic hypotension sub-score.
compass_pupil	numeric	COMPASS-31 pupillomotor sub-score.
compass_sudor	numeric	COMPASS-31 sudomotor (sweating) sub-score.
compass_totale	numeric	Total COMPASS-31 autonomic dysfunction score.
compass_uin	numeric	COMPASS-31 urinary sub-score.
compass_vasc	numeric	COMPASS-31 vasomotor sub-score.

Column	Type	Short explanation
delta_off_on	numeric	Difference between UPDRS_OFF and UPDRS_ON (treatment effect).
durata_malattia	numeric	Disease duration from onset (years).
eta_attuale	numeric	Current patient age.
eta_diagnosi	numeric	Age at diagnosis.
eta_esordio	numeric	Age at first motor symptom.
h_and_y	numeric	Hoehn & Yahr stage (1–5).
ledd	numeric	Levodopa equivalent daily dose (mg/day).
ledd_per_anno	numeric	LEDD normalized per year of disease.
n_anomalie_mri	numeric	Number of abnormal MRI findings.
n_red_flags_msa	numeric	Count of MSA “red-flag” features (per MDS).
n_red_flags_msa_clinic_certified	numeric	Clinically certified number of red flags.
parkinsonism	numeric	Severity/composite score of parkinsonian signs (rigidity, bradykinesia, tremor).
percentuale_risposta_ldopa	numeric	% improvement after acute L-Dopa test.
progression_rate	numeric	Calculated progression speed (e.g. H&Y / disease years).
ritardo_diagnostico	numeric	Diagnostic delay (years from symptom onset to diagnosis).
updrs_off	numeric	UPDRS-III motor score in OFF-medication state.

Column	Type	Short explanation
updrs_on	numeric	UPDRS-III motor score in ON-medication state.
atrofia_cervelletto	binary	MRI: cerebellar atrophy.
atrofia_del_putamen	binary	MRI: putaminal atrophy.
atrofia_peduncoli_cerebellari_medi	binary	MRI: middle cerebellar peduncle atrophy.
atrofia_ponte	binary	MRI: pontine atrophy.
behavioural_alteration	binary	Behavioural or personality changes.
caduta_segnaled_putamen	binary	MRI: putaminal signal loss on T2*/SWI.
cadute	binary	History of falls.
carrozzina	binary	Wheelchair use.
cerebellar_syndrome	binary	Presence of cerebellar signs (ataxia, dysmetria).
cognitive_decline	binary	Cognitive impairment or dementia.
cold_discolored_hands_and_feet	binary	Peripheral vasomotor disturbance (autonomic).
constipation	binary	Chronic constipation.
craniocervical_dyst_induced_dy_l_dopa	binary	Craniocervical dystonia induced by L-Dopa.
deambulaz_appoggio	binary	Ambulates with support.
deambulaz_autonoma	binary	Ambulates independently.
drooling	binary	Hypersalivation / drooling.
erectile_disfunction	binary	Erectile dysfunction (autonomic)

Column	Type	Short explanation
		symptom).
fatigue	binary	Fatigue / lack of energy.
hot_cross_bun_sign	binary	MRI: pontine cruciform hyperintensity typical of MSA-C.
hyposmia	binary	Reduced sense of smell.
inspiratory_sighs	binary	Sighing or irregular breathing pattern.
iperintensita_peduncoli_cerebellari_medi	binary	MRI: MCP hyperintensity.
iperintensita_putamen	binary	MRI: putaminal hyperintensity.
jerky_myoclonic_postural_or_kinetic_tremor	binary	Irregular / jerky tremor type.
moderate_to_severe_postural_instability_w_3_yrs_of_motor_onset	binary	Postural instability within 3 years of motor onset.
normal_rmn	binary	Normal brain MRI.
pain	binary	Chronic or neuropathic pain.
pathologic_laughter_or_crying	binary	Emotional incontinence (pseudobulbar affect).
poor_l_dopa_responsiveness	binary	Poor or absent clinical response to L-Dopa.
postural_deformities	binary	Axial/postural deformities (camptocormia, Pisa).
rapid_progression_w_3_yrs	binary	Rapid disease progression within 3 years.
rbd	binary	REM sleep behavior disorder.
russamento_osas	binary	Snoring / sleep apnea (OSAS).
severe_dysphagia_w_3_yrs	binary	Severe dysphagia within 3 years of

Column	Type	Short explanation
		onset.
severe_speech_impairment_w_3_yrs	binary	Severe dysarthria within 3 years of onset.
sonnolenza_diurna	binary	Excessive daytime sleepiness.
stridor	binary	Laryngeal stridor (inspiratory noise).
unexplained_babinski	binary	Pathological Babinski sign unexplained by stroke.
unexplained_urinary_urge_incontinence	binary	Urinary urge incontinence unexplained by obstruction.
unexplained_voiding_difficulties	binary	Urinary retention / difficulty voiding unexplained by prostate disease.
visual_alteration	binary	Visual disturbances or blurring.
anamnestic_oh	binary	History of orthostatic hypotension from anamnesis.
diagnosi_definita	categorical	Final confirmed diagnosis (PD / MSA-P / MSA-C / Control).
diagnosi_di_invio	categorical	Referral diagnosis at first evaluation.
gruppo_eta	categorical	Age group (e.g. <50, 50-60, 60-70, >70).
sezzo	categorical	Sex (M/F).
stadio_malattia	categorical	Disease stage grouping (e.g. early / mid / late).
data_di_nascita	date	Full birth date.

pointed by Grazia


Set	Variables Included
Clinician-Certified MSA Red Flags	<p>poor_l_dopa_responsiveness , rapid_progression_w_3_yrs , moderate_to_severe_postural_instability_w_3_yrs_of_motor_onset , craniocervical_dyst_induced_dy_l_dopa , severe_speech_impairment_w_3_yrs , severe_dysphagia_w_3_yrs , unexplained_babinski , jerky_myoclonic_postural_or_kinetic_tremor , postural_deformities , unexplained_voiding_difficulties , unexplained_urinary_urge_incontinence , stridor , inspiratory_sighs , cold_discolored_hands_and_feet , pathologic_laughter_or_crying</p>

2. Data Ingestion and Harmonization


- Load clinical csv (harmonizing different representations of missing values to Nan)
- Column names normalized: Unicode stripped, whitespace collapsed, then slugified to ASCII snake_case.
- Diagnosis labels trimmed and harmonized (e.g., MSA-P/C → MSA-P).
- Numeric casting based on patterns; categorical cleaning (uppercasing, NA handling).
- Duplicates check

3. Missingness Profiling

- Quantify missingness per variable per class to guide usable features.


 Missingness by variable

 Missing PD  Missing MSA

 **NOTE:** which threshold do i keep?

 **IMPORTANT:** Note that PD has much more missings

Remaining columns after removal of high missing columns

 remaining_columns

4. Derived Variables and Cleaning

- Create analysis-friendly fields (examples):
 - Timing/severity: eta_attuale , eta_esordio , durata_malattia , percentuale_risposta_ldopa .
 - Aggregates: n_red_flags_msa , n_anomalie_mri as the sum of the corresponding binary symptoms columns

Variable	Short description
eta_attuale	Current patient age.
ritardo_diagnostico	Diagnostic delay (years from symptom onset to diagnosis).
anni_dalla_diagnosi	Years elapsed since formal diagnosis.
percentuale_risposta_ldopa	% improvement after acute L-Dopa test.
ledd_per_anno	Levodopa equivalent daily dose normalized per year of disease.
n_red_flags_msa	Count of MSA "red-flag" AI generated.
n_red_flags_msa_clinic_certified	Clinically certified count of MSA red flags.
n_anomalie_mri	Number of abnormal MRI findings.
stadio_malattia	Disease stage grouping (e.g. early / mid / late).
gruppo_eta	Age group (e.g. <50, 50-60, 60-70, >70).
progression_rate	Calculated progression speed (e.g. H&Y / disease years).

5. Outlier Detection

- Use Tukey's fences on key continuous variable to spot extreme values.
- Provides a record of suspected outliers for clinician review.

Method: Tukey's Fences


- Lower fence = $Q1 - 1.5 \times IQR$
- Upper fence = $Q3 + 1.5 \times IQR$
- Values outside these fences are flagged as outliers


 Outlier distributions  Outlier Summary Table


 **TODO:** Make clinician verify outliers and decide what to do with those


6. Cohort Overview

- Distribution of patients across definitive diagnoses.
- A compact summary table (N, M/F, age at onset, duration, current age).

 Patient distribution by diagnosis

 diag barchart

 **WARNING:** PD patients are predominantly males

diag barchart

violin_plots


diag barchart diag barchart

7. Multi-symptoms clusters and Co-occurrence

This analysis identifies and visualizes patterns of symptom co-occurrence within each diagnostic group (MSA-P, MSA-C, PD) to reveal characteristic multi-symptom profiles that may aid differential diagnosis.

Rationale: While univariate symptom prevalence identifies individual discriminators, parkinsonian syndromes are clinically characterized by specific constellations of concurrent symptoms.

Symptom clusters (UpSet view)

Symptom clusters 2 (UpSet view)

Symptom clusters 3 (UpSet view)

Symptom clusters 4 (UpSet view)

7.1 symptoms co-occurrence heatmaps

This analysis quantifies pairwise symptom co-occurrence within each diagnostic group using the Jaccard similarity coefficient, revealing which symptoms tend to appear together in **individual patients**.


Methods:


- **Jaccard index:** For each symptom pair, computed as the ratio of co-occurrence (intersection) to total presence (union): $J(A,B) = |A \cap B| / |A \cup B|$
- **Scale:** Ranges from 0 (symptoms never co-occur) to 1 (perfect overlap—every patient with symptom A also has symptom B, and vice versa)

Symptom co-occurrence (Jaccard)

Symptom co-occurrence (Jaccard)

Symptom co-occurrence (Jaccard)

Symptom co-occurrence (Jaccard)

 **NOTE:** PD heatmaps lacks columns of the symptoms which are always not expressed (ie set to 0)

8. Motor Function and L-Dopa Responsiveness

Objective: Compare motor severity (UPDRS OFF) and treatment response across diagnoses.
higher UPDRS values means severe motor impairment

Clinical Relevance:

- **UPDRS OFF score:** Measures motor impairment without medication, reflecting disease severity
- **L-dopa responsiveness: KEY DIAGNOSTIC CRITERION** distinguishing MSA from PD
 - PD: Typically >30% improvement with L-dopa (good response)
 - MSA: Poor L-dopa response (<30% improvement) is a core diagnostic feature

Clinical Importance: This is one of the most critical clinical differentiators between MSA and PD

Expected Findings:

- Similar or higher UPDRS OFF scores in MSA (more severe motor impairment)
- Significantly lower L-dopa response in MSA vs. PD
- High inter-individual variability, especially in MSA

Results

- expected finding one and two are respected (can also be seen by the slope of the graph plotting values of UPDRS OFF and ON)
- although MSA-P presents outliers it doesn't show higher variability than PD

 Symptom clusters (UpSet view)

 Symptom clusters (UpSet view)

9. MSA Red Flags and Hoehn & Yahr Severity

Objective: Quantify MSA-specific clinical red flags and assess disease staging.

Clinical Relevance:

- **Red flags:** Clinical features suggestive of MSA (e.g., rapid progression, early autonomic failure, poor L-dopa response, cerebellar signs)
- **Hoehn & Yahr (H&Y) staging:** Standard PD staging system (0-5), also applicable to parkinsonian disorders
 - Stage 1-2: Unilateral/bilateral involvement, no balance impairment
 - Stage 3: Balance impairment, physically independent
 - Stage 4-5: Severe disability, wheelchair-bound



Red flags and H&Y severity



IMPORTANT: MSA patients are overwhelmingly in worse disease stages than PD ones

10. Diagnostic Delay and Progression

Objective: Quantify time from symptom onset to diagnosis and calculate progression rates.

Clinical Relevance:

- **Diagnostic delay:** Time between symptom onset and formal diagnosis
 - Reflects diagnostic complexity and symptom overlap between conditions
 - Longer delays may indicate atypical presentations
- **Progression rate:** Speed of clinical decline (e.g., H&Y stage change per year)
 - MSA progresses faster than PD (key differentiator)
 - Rapid progression within 3 years is an MSA red flag

Expected Findings:

- MSA may show longer diagnostic delays due to initial misdiagnosis as PD
- MSA demonstrates faster progression rates than PD
- High variability in both measures reflects diagnostic complexity

Results Analysis

- all expected findings are respected  Diagnostic delay and progression

11. MRI Abnormalities (Supportive Features)


- Total abnormality count by diagnosis; specific signs: hot-cross-bun, putamen atrophy/signal changes.
- Clinical reading: MSA-C shows pontocerebellar signs; MSA-P shows putaminal changes; PD often near-normal MRI.

MRI findings comparison

12. Autonomic Dysfunction Profile (COMPASS)

- Compare subscales COMPASS across classes.

COMPASS subscales comparison

 **IMPORTANT:** COMPASS is a high missing value (almost 40%) especially for PD patients where almost 80% of them do not have a compass value

13. Univariate Screening and Mutual Information

Since the dataset contains both continuous (with different distribution) and categorical features proper statistical tests on early diagnoses features (ie features that a patient could present before being diagnosed/at first clinical visit) to understand which of those are statistically more relevant to distinguish diagnoses class and could potentially be integrated into a ML model.

- For each feature: appropriate test (ANOVA/Welch/Kruskal for continuous (decision based on feature distribution ie if they respect normality and homoscedacity); Chi-square for binary).
- Effect sizes and p-values aggregated and adjusted using FDR (Benjamini-Hochberg False Discovery Rate)
- **Mutual Information (MI)** is computed for each feature to quantify any **non-linear dependencies** between that variable and the diagnosis, beyond what ANOVA captures.
- A combined visualization summarizes top features by q-value/effect and MI.
- the best top K(=10) features (for both MI and ANOVA/Kruskal) are taken to be used with ML model.

Feature importance analysis

importance analysis

14. Differential and Within-Diagnosis Correlations


- Differential correlations: identify pairs of continuous variables whose association differs between diagnoses.
- Within-diagnosis correlation heatmaps (MSA-P, MSA-C, PD) for key clinical variables.

Method:

1. Calculate correlation matrices **separately** for each diagnosis (MSA-P, MSA-C, PD)
2. For each variable pair, compute the **maximum absolute difference** in correlation coefficients across groups:

$$\text{Max Diff} = \max \left(|r_{\text{MSA-P}} - r_{\text{PD}}|, |r_{\text{MSA-C}} - r_{\text{PD}}|, |r_{\text{MSA-P}} - r_{\text{MSA-C}}| \right)$$

3. Rank pairs by Max Diff to identify **most differentially correlated** relationships

 Differential correlations

Main Insights

- **Autonomic-Structural Link**

Compass Totale increases with *N° Anomalie MRI* only in **MSA-P**, suggesting that structural damage (putamen/cerebellum) parallels autonomic failure — absent in PD.

strange MSA-C inverse correlation.

- **Disease Duration Effect**

Compass Totale rises with *Durata Malattia* in PD and MSA-C indicating **progressive autonomic decline**

strange MSA-P inverse relationship

- **Medication Dynamics**


- In PD, *LEDD* scales with disease duration (normal titration).
- In MSA, higher *LEDD* does **not** improve *Compass Totale* or *Progression Rate* as much as it does for PD patients consistent with **poor dopaminergic responsiveness** of MSA.

- **Motor-Autonomic Coupling**




H&Y correlates positively with *Compass Totale* and *Progression Rate* in MSA, but not in PD supporting **parallel motor and autonomic progression** in MSA.

- **Diagnostic Red Flags**

Patients with low % *L-dopa response* show more *MSA red flags*, consistent with **poor dopaminergic responsiveness** of MSA.

 **IMPORTANT:** COMPASS is a high missing value (almost 40%) especially for PD patients where almost 80% of them do not have a compass value

Within diagnosis symptoms correlation (Pearson)

 Correlation heatmap (MSA-P)  Correlation heatmap (MSA-C)  Correlation heatmap (PD)

15. ML model integration

Highly discriminative easy-to-collect features are selected (selected in step 13):

- 'unexplained_urinary_urge_incontinence'
- 'russamento_osas'
- 'anamnestic_oh'
- 'sonnolenza_diurna'
- 'cold_discolored_hands_and_feet'
- 'cerebellar_syndrome'
- 'postural_deformities'
- 'parkinsonism'
- 'constipation'
- 'jerky_myoclonic_postural_or_kinetic_tremor'


few simple ML/statistical models are used to make predictions.


- dummy = random guess
- logistic regression (logreg)
- random forest (rf)


8 fold cross validation is performed

The **Matthews Correlation Coefficient (MCC)** is included as a key metric for model evaluation instead of f1.

- **MCC** is a balanced measure, even for imbalanced classes, giving a value between -1 (inverse prediction) and +1 (perfect prediction); 0 indicates random performance.

 model comparisons

OUT OF FOLD CONFUSION MATRIX aggregates prediction for each test fold data. ie these are the prediction aggregated over each fold test set  model conf_matrix

 **TODO:** Clinician features review