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# Beyond BMI: Unsupervised Machine Learning Clustering of Bioelectrical Impedance Phenotypes Is Associated With Weight-Recovery Trajectories in Anorexia Nervosa

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## ABSTRACT

**Objective:** To identify data-driven body composition phenotypes in patients with moderate-to-extreme anorexia nervosa (AN) using machine learning (ML) clustering of bioelectrical impedance analysis (BIA) parameters, and to test whether these phenotypes have specific psychopathological and childhood trauma profiles while correlating with early weight-recovery trajectories.

**Method:** In a prospective observational cohort, 100 females (18–40 years) with AN and body mass index (BMI) < 17 kg/m$^2$ were enrolled. Baseline BIA-derived measures (phase angle, body cell mass, fat mass, fat-free mass, total body water, and extracellular water) were clustered using Unsupervised Random Forest algorithms and consensus-based selection of the optimal number of clusters. Between-cluster differences were tested, and longitudinal BMI trajectories were modeled with generalized additive mixed models across weekly follow-ups up to 3 months.

**Results:** Three clusters emerged ($n$ = 23, 53, 24) with separation driven primarily by hydration and lean-mass indices (total body water, fat-free mass, body cell mass), yielding phenotypes consistent with "Preserved Body Cell Mass", "Severe Depletion", and "Fluid Redistribution" (elevated extracellular water with low body cell mass and phase angle), despite overlapping BMI. Clusters 1 and 2 showed higher childhood trauma exposure and specific trait differences. At 3 months, Cluster 3 showed a more pronounced BMI increase over time than Clusters 1 and 2.

**Discussion:** BIA-based ML phenotyping may complement current BMI-centric severity staging by capturing distinct morpho-functional patterns associated with differential early weight-recovery trajectories. BIA provides a noninvasive low-cost assessment, supporting more personalized nutritional and psychotherapeutic planning and informing future precision-staging research in AN.

**Key Points**

- In a sample of 100 adult females with moderate-to-extreme anorexia nervosa, unsupervised machine learning clustering of bioelectrical impedance analysis (BIA) parameters identified three distinct body composition phenotypes: "Preserved Body Cell Mass," "Severe Depletion," and "Fluid Redistribution", despite overlapping BMI values across groups.
- The three phenotypes showed divergent early weight recovery trajectories over 3 months: the "Fluid Redistribution" cluster achieved the more pronounced BMI gain, while the other two showed the most limited recovery, suggesting that hydration status and cellular integrity, rather than BMI or caloric intake alone, may serve as relevant indicators for clinical staging.
- Clusters with poorer weight recovery were characterized by greater exposure to childhood traumatic experiences and specific trait differences, consistent with the maltreated ecophenotype of anorexia nervosa and its known resistance to standard treatments.
- If confirmed in larger studies, these exploratory findings suggest that integrating BIA-derived body composition parameters with psychobiological profiling could complement standard BMI-based assessment, with possible implications for personalized nutritional and psychotherapeutic interventions in clinical practice.

## 1 | Introduction

Anorexia nervosa (AN) is a life-threatening eating disorder (ED) defined by three core features: persistent restriction of energy intake, an intense fear of gaining weight or becoming fat (or persistent behavior that interferes with weight gain), and a distorted perception of one's body weight or shape (American Psychiatric Association 2022). It is a multifactorial and complex condition involving biological, psychological, and social factors contributing to its onset and progression (Russell 2020). Despite advances in evidence-based treatments, relapse rates remain as high as 40% (de Rijk et al. 2024), leading to a high burden on specialized care services (Castellini et al. 2023, 2024).

Currently the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), along with its text revision (DSM-5-TR), retains only a severity specifier for adult AN based largely on body mass index (BMI) (American Psychiatric Association 2022). However, numerous studies have questioned the clinical utility of BMI as a sole indicator of severity, given its limited sensitivity in assessing both the initial severity state and the longitudinal course of the disease (Dang et al. 2023; Toppino et al. 2022; Dalle Grave et al. 2018). Specifically, the well-documented limitations of BMI include its inability to accurately represent body composition, especially in AN, where significant reductions in fat mass (FM), fat-free mass (FFM), and bone mass are common (Hübel et al. 2019; Tarchi et al. 2025). For example, a loss of body cell mass, which includes proteins and intracellular water, might not be detected by weight alone since an increase in extracellular fluid could compensate for it, particularly in cases of severe malnutrition (Jaffrin and Morel 2008). Moreover, while BMI can offer a rough estimate of nutritional status, it falls short in capturing the psychopathological complexity of the disorder, as highlighted by a recent systematic review and meta-analysis (Dang et al. 2023). From a disease staging perspective, while initial BMI (on which the DSM bases its severity specifiers) typically predicts discharge weight due to autoregression (Meule et al. 2025), it often shows limited predictive value for long-term psychopathological and sustained weight recovery outcomes (Toppino et al. 2022; Dalle Grave et al. 2018).

These limitations have driven growing interest in redefining psychiatric staging systems by integrating more accurate outcome predictors and clinical specifiers. These efforts aim to capture a broader range of signs and symptoms, account for individual variability, and reflect the complex interplay between biological and psychological factors (Tomba et al. 2024). This approach parallels developments in clinical oncology, where highly advanced staging models guide both treatment strategies and prognostic evaluations (Hyam et al. 2023). Consequently, in recent years there has been a major effort to identify biological markers and clinical profiles that allow a better characterization of AN and its prognosis (Dani et al. 2024; Rossi, Cassioli, Cecci, et al. 2024). A primary example of this shift is the proposal of a new diagnostic specifier, the "maltreated ecophenotype". This subtype is characterized by distinct clinical-biological features and a poorer response to standard treatment (Rossi, Cassioli, Cecci, et al. 2024; Rossi, Cassioli, Dani, et al. 2024), likely mediated by the impact of early life stress on the neuroendocrine and immune systems (Rossi, Cassioli, Dani, et al. 2024; Rossi et al. 2021). Specifically, childhood trauma has been linked to hypothalamic–pituitary–adrenal (HPA) axis dysregulation and chronic low-grade inflammation (Rossi, Cassioli, Dani, et al. 2024; Rossi et al. 2021). These processes can significantly alter metabolic pathways and, consequently, body composition and fluid distribution (Rossi, Cassioli, Dani, et al. 2024; Zhu et al. 2026). Therefore, investigating trauma history alongside biological data is essential to determine if environmental stressors are associated with specific metabolic clusters. However, despite these conceptual advances, the field still lacks concrete data for a formalized AN staging system based on both psychopathological distinctive features and specific biomarkers. Identifying different disease trajectories remains a challenge because standard clinical tools cannot capture this biological complexity.

Within the assessment of nutritional status, bioelectrical impedance analysis (BIA) offers a more nuanced understanding of body composition compared to BMI. While dual-energy X-ray absorptiometry (DEXA) remains the gold standard (Lee and Gallagher 2008), its cost and accessibility constraints make BIA a more practical alternative in clinical settings (Tewari et al. 2018). BIA works by passing a low-level, safe electrical current through the body and directly measuring its electrical impedance, specifically resistance and reactance (Lee and Gallagher 2008). From these raw measurements, predictive equations are used to estimate total body water (TBW), FFM, and FM, because lean tissues conduct electricity more readily than adipose tissue owing to their higher water and electrolyte content. Phase angle (PhA), calculated from the relationship between resistance and reactance, provides an additional qualitative marker of cellular membrane integrity and cellular

health rather than a direct measure of body composition. More detailed compartmental analysis may also distinguish body cell mass (BCM), which represents metabolically active protein-rich tissue, from extracellular water (ECW), which reflects the fluid compartment outside cells.

BIA's ability to provide parameters describing body composition allows for a comprehensive picture of mass and fluid redistribution in the severe underweight condition characterizing patients with AN (Moonen and Van Zanten 2021), extending well beyond what is possible with BMI alone. This comprehensive assessment is particularly achievable through advanced techniques such as those based on machine learning (ML), which account for multiple parameters simultaneously and overcome the inherent limitations of considering a single parameter at a time. For example, a recent study using ML-based clustering on BIA parameters identified different metabolic phenotypes in overweight populations with similar BMI (Xiang et al. 2025).

Considering that a similar approach has never been adopted in AN, the aim of this study was to identify different clusters in a group of patients with moderate to extreme AN (BMI < 17 kg/m$^2$) using ML-based techniques on body composition parameters, and to examine the association between baseline cluster membership and subsequent early weight-recovery trajectories over 3 months through serial longitudinal BMI assessments. Additionally, the possible overlap of this clustering with different psychopathological, behavioral, and childhood trauma profiles was also investigated.

## 2 | Method

This was a prospective observational study with serial dietitian follow-ups for a maximum of 3 months from the first assessment.

### 2.1 | Sample

A naturalistic cohort of female patients who attended the ED Unit of Careggi University Hospital in Florence seeking outpatient care was enrolled between March 2022 and December 2024, provided they met the following inclusion criteria: (1) female sex, (2) age between 18 and 40 years, (3) BMI under 17 kg/m$^2$, (4) diagnosis of AN according to the DSM-5 American Psychiatric Association (2022), as assessed by the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV) (Shabani et al. 2021). Exclusion criteria were as follows: (1) illiteracy, intellectual disability, (2) presence of psychotic symptoms, severe depression, or manic state at the time of enrollment, current suicidal ideation, (3) severe medical conditions precluding treatment in an outpatient context, and (4) lack of written informed consent. Of the 172 patients with AN referred, 60 subjects were excluded because of the following reasons: severe depression with suicidal ideation ($n = 4$), severe medical conditions ($n = 4$), refusal to sign the consent and to participate ($n = 6$), BMI over 17 kg/m (Russell 2020) ($n = 46$). Additionally, 12 subjects were found to be lost to follow-up or dropped from treatment after the initial assessment. Given the longitudinal design of the study, only patients with complete data at both baseline and follow-up assessment ($n = 100$) were included in the final statistical analyses. Baseline characteristics of the excluded subjects did not differ significantly from those of the patients who completed the assessments required by the study (Table S2).

The protocol was approved by the Ethics Committee of the organizing institution, and the study was conducted in accordance with the Declaration of Helsinki. This study was conducted and reported in accordance with the STROBE guidelines for observational cohort studies (Von Elm et al. 2007).

### 2.2 | Study Design and Assessment

Patients were first evaluated by expert psychiatrists in the field of EDs (E.C., G.C., E.R.) collecting sociodemographic and clinical data and administering the clinical interview for DSM-5 diagnoses. Eligible patients with AN were then offered clinical programs at the same clinic. The clinical program was planned as follows. First, patients were admitted to the Day Hospital of the clinic. On their first day at the clinic anthropometric data, including height and weight, were collected using calibrated scales under the supervision of a female operator to minimize manipulation. Their body composition was also assessed at the time of first evaluation by a dietitian through BIA. In this context, a 24-h dietary recall was conducted in order to characterize baseline nutritional intake. This assessment included a detailed semi-quantitative analysis of all food and fluid consumption from the previous day to estimate total energy intake (kcal/day) and macronutrient distribution (carbohydrates, proteins, and lipids). This procedure allowed to verify that differences in body composition phenotypes were not primarily driven by acute variations in caloric intake. Additionally, the timing and composition of the last meal were recorded to ensure compliance with requirements for BIA standardization (more details below). The second phase of the dietary intervention involved the development of an individualized nutritional plan, which included meals and/or oral nutritional supplements. Patients were offered a five-meal plan to be consumed within the treatment facility. All patients participated in assisted meal procedures under the supervision of healthcare professionals trained in managing mealtime-related challenges (Kells et al. 2013). This structured therapeutic approach for EDs aimed to regulate appetite, satiety, and body weight. It supported patients in gradually recognizing and responding to biological hunger cues, adapting to environmental challenges, and dismantling distorted beliefs about food (Hackert et al. 2020).

From a psychotherapeutic perspective, all patients began an individual psychotherapy program using enhanced cognitive behavioral therapy (CBT-E) from the start of treatment. The patients attended weekly sessions with CBT therapists who had completed the official web-centered certified training in CBT-E from the Centre for Research on EDs at Oxford (CREDO), and who regularly participated in supervision with supervisors experienced in the treatment of EDs. All described interventions were part of standard clinical practice and were not altered by participation in the current study.

Following the baseline assessment, participants were re-evaluated weekly by a dietitian for a period of three months as

part of the standard clinical protocol for nutritional rehabilitation. These weekly sessions included weight monitoring and clinical evaluation to track progress. Given that the maximum follow-up in this study (3 months) did not coincide with the end of treatment, partial weight restoration was considered the longitudinal outcome. Since validated thresholds for defining whether this outcome was achieved or not were not available, the average BMI gains for early responders reported in a previous study using a similar clinical setting and a comparable treatment duration were used as references (Wade et al. 2021). Specifically, an increase in BMI of at least 0.63 compared to baseline was used as the moderate early response threshold, and an increase of at least 1.56 was used as the rapid early response threshold (Wade et al. 2021).

#### 2.2.1 | Psychometric Measures

All participants underwent clinical and psychometric evaluation during the initial psychiatric visit. The following self-administered instruments were used in their validated Italian versions:

- The Brief Symptom Inventory, a 53-item scale for the assessment of general psychopathology levels. The average of all items provides a general index of psychopathology, the Global Severity Index (Derogatis and Melisaratos 1983). In the current study, the internal consistency was $\alpha = 0.97$.
- The Eating Disorder Inventory-2 (EDI-2) is a 91-item self-report questionnaire designed to assess different eating-disorder–related domains. Items are rated on a six-point Likert scale and are organized into 11 subscales: drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, and social insecurity (Garner 1991). For this sample, overall internal consistency was $\alpha = 0.97$.
- The Eating Disorder Examination Questionnaire 6.0 (EDE-Q 6.0) is a 28-item self-report questionnaire rated on a seven-point Likert scale that assesses the range, frequency, and severity of eating-disorder–related behaviors and psychopathology. The global score (EDE-Q Total Score) was used for analysis, with an internal consistency of $\alpha = 0.91$ in this study (Calugi et al. 2017).
- The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report measure designed to assess exposure to traumatic experiences during childhood, including emotional neglect and abuse, sexual abuse, physical neglect, and abuse. Item scores can be summed to obtain a Total Score (Bernstein et al. 2003). The internal consistency was $\alpha = 0.95$.

### 2.3 | BIA

With respect to BIA, a multi-frequency segmental body composition analyzer (Akern BIA 101, BIVA PRO) was used to obtain whole and compartmental body composition data. To ensure data accuracy and minimize the influence of recent intake or posture on fluid distribution, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines were followed (Kyle, Bosaeus, De Lorenzo, et al. 2004). Specifically, all measurements were conducted in the morning in a climate-controlled room (20°C–24°C) following an 8-h fast, abstinence from strenuous physical activity for at least 12 h, and after participants had voided their bladders. Participants were asked to lie in a supine position on a flat mattress for at least 5 min prior to the assessment to allow for body fluid equilibration. Tetrapolar surface electrodes were placed on the right hand and right foot according to standard anatomical landmarks, and a single BIA measurement was recorded for each participant. Clinical examination confirmed the absence of overt peripheral edema, and no participants were receiving medications known to directly alter fluid retention (e.g., diuretics, systemic corticosteroids). Given the undernutrition status of the sample (BMI < 17.0 kg/m$^2$), all participants exhibited secondary amenorrhea, limiting potential menstrual cycle-related hydration variations. All BIA measurements were performed under identical conditions for all participants. Six indices of body composition were calculated: one raw bioelectrical parameter (PhA), and five equation-derived estimates (BCM, FM, FFM, TBW, and ECW) (Kyle, Bosaeus, De Lorenzo, et al. 2004). PhA is the relationship between the electrical current passing through the body and the potential difference induced by current across the body tissue. PhA is currently accepted as a prognostic indicator of morbidity and mortality (Popiołek et al. 2019). Conversely, the remaining parameters represent equation-derived estimates based on population algorithms. BCM is an indicator of nutritional status, and assesses the weight of metabolically active mass, distinguishing between total body weight and the effect of ECW (Earthman et al. 2007). FM and FFM represent the body weight of the respective components (Jaffrin 2009). Body fluid volume, represented by TBW, is strongly related to FFM, which assumes a standard hydration fraction of 73.2% water. It is important to note that this assumption may be strained by fluid shifts in severe AN. ECW refers to the portion of TBW that exists outside the body's cells. Height-squared normalized ratios were then computed according to established methods (Kyle, Bosaeus, De Lorenzo, et al. 2004).

### 2.4 | Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD) or as median [25th–75th percentiles], where appropriate.

To identify data-driven phenotypes based on body composition parameters, we employed an Unsupervised Random Forest (URF) algorithm, with 10,000 trees to reduce variability in the estimated proximity matrix (Shi and Horvath 2006; Liaw and Wiener 2002). Clustering was performed exclusively on BIA-derived variables, specifically: FFM, FM, BCM, TBW, ECW, and PhA. All variables, except for PhA, were entered into the model normalized by body surface area.

The optimal number of clusters ($k$) was determined using the NbClust package, which computes 26 distinct cluster validity

indices (Charrad et al. 2014). Because different indices can evaluate cluster quality differently (some prioritizing compactness, others separation), relying on a single index can be misleading. NbClust aggregates the results of all 26 indices and applies a 'majority rule,' where the optimal number of clusters is the *k* value that receives the highest number of votes across all indices. This consensus approach is widely recognized as a robust method for mitigating the bias of individual metrics (Charrad et al. 2014). In addition, the final number of clusters was selected as the one that was not only supported by the majority rule of the validity indices, but also associated with the lowest Bayesian Information Criterion (BIC), thus favoring the most parsimonious and best-supported clustering solution. Internal validation of the cluster solution was performed using the Silhouette width, which measures how similar an object is to its own cluster (cohesion) compared to other clusters (separation) (Rousseeuw 1987). A silhouette width close to one implies appropriate classification, while negative values indicate potential misclassification (Rousseeuw 1987). An average silhouette width of less than 0.20 should be interpreted as a lack of substantial cluster structure (Everitt et al. 2011), whereas a value greater than 0.25 is considered acceptable (Kaufman and Rousseeuw 1990). Any cases yielding negative silhouette widths were retained in all subsequent analyses rather than being excluded. This was made to preserve the ecological validity of the sample, recognizing that clinical and biological phenotypes naturally present with overlap and boundary cases. Excluding such individuals would artificially inflate cluster separation and compromise the real-world generalizability of the findings. To visualize the high-dimensional structure of the identified subgroups in a lower-dimensional space, we utilized t-Distributed Stochastic Neighbor Embedding (t-SNE) (2D and 3D projections) (van der Maaten and Hinton 2008). To formally evaluate the dataset's clustering tendency and test against the null hypothesis of a uniform, non-clustered distribution, the Hopkins statistic (*H*) was calculated. A Hopkins statistic value above 0.50 indicates non-random data structure, while values exceeding 0.75 denote strong clustering tendency (Lawson and Jurs 1990). Finally, in order to estimate the contribution of each biological feature to the definition of the clusters, we calculated the Mean Decrease Gini, a measure of variable importance derived from the Random Forest algorithm (Liaw and Wiener 2002).

The URF clustering technique was selected because it generates an individual-level proximity matrix from the multivariable patterns of BIA measures; this matrix can subsequently be used to identify clusters of patients with similar biological profiles (Shi and Horvath 2006; Liaw and Wiener 2002). Unlike approaches based exclusively on direct Euclidean distances, this proximity-based framework can accommodate correlated variables and potentially non-linear or interactive relations (Shi and Horvath 2006; Liaw and Wiener 2002). This characteristic was relevant to BIA parameters, which reflect interdependent body-composition and fluid compartments rather than independent biological dimensions. The use of URF was therefore considered more appropriate in this context, in order to capture multivariable patterns of biological similarity among patients. Given the modest sample size and the restricted number of input variables, the resulting cluster solution was interpreted as exploratory and internally assessed. Cluster labels were designated post hoc as descriptive operational categories based on relative BIA parameters rather than pathophysiological entities.

Differences between the identified clusters regarding body composition were investigated using Analysis of Variance, whereas BMI-adjusted Analysis of Covariance (ANCOVA) was used for comparing baseline demographics and psychopathological variables. For non-continuous variables, rank ANCOVA was used. Post hoc pairwise comparisons were conducted using the Tukey method. The frequency of childhood abuse and neglect and the proportions of AN subtypes were compared across clusters using Fisher's exact test, with post hoc analyses adjusted according to Benjamini and Hochberg to control the false discovery rate.

To analyze weight recovery trajectories over time, Generalized Additive Mixed Models (GAMMs) were employed. This approach was chosen to account for potential non-linearities in the recovery trends and the nested structure of the data (repeated measures within subjects). The model specification included BMI as the dependent variable. The temporal trend was modeled using a thin plate regression spline for the time variable, with Cluster entered as both a parametric fixed effect (to test intercept differences) and a grouping factor for the smooth terms. This Cluster × smooth interaction allowed to estimate a reference smooth for the baseline cluster and difference smooths for the other clusters, thereby testing whether the shape of the recovery trajectory differed significantly between phenotypes. A random intercept was included. Longitudinal GAMM analyses were restricted to participants with complete assessments across the planned 3-month follow-up. Although GAMMs can accommodate unbalanced repeated observations, participants who discontinued treatment contributed data only during the early treatment phase and no observations during the latter follow-up period. The complete-case approach was therefore used to estimate cluster-specific trajectories over a common, fully observed 3-month time window (Mundo et al. 2022). For post hoc comparisons between all three clusters, a model rotation strategy was used: the GAMM was refitted with each cluster set sequentially as the reference category, in order to test the statistical significance of every between-Cluster smooth difference. Finally, to rule out the potential confounding effect of initial severity, a sensitivity analysis was performed by adding baseline BMI as a linear covariate to the model structure (Model 4). For each GAMM, EDF were reported to describe the complexity of the smooth terms (where EDF≈1 indicates a linear relationship and EDF > 1 indicates non-linearity) and the F-statistic for significance testing.

All statistical tests were two-tailed, and the significance level was set at $p < 0.05$. Analyses were performed with R Statistical Software version 4.4.3 (R Core Team 2025), and the following libraries: cluster, ggplot2, mgcv, NbClust, randomForest, Rtsne (Liaw and Wiener 2002; Charrad et al. 2014; van der Maaten and Hinton 2008; Maechler et al. 2024; Wickham 2016; Wood 2011).

### 2.5 | Lived Experience Involvement Statement

No specific efforts were undertaken to involve persons with lived experience in the study design or execution, or in the preparation of this manuscript.

## 3 | Results

A total of 100 patients suffering from moderate to extreme AN (BMI < 17.00 kg/m$^2$) were enrolled in this study (57 of the Restricting subtype, and 43 of the Binge-eating/purging subtype). Descriptives regarding their general and psychopathological characteristics are reported in Table 1.

### 3.1 | Unsupervised Random Forest Clustering

The Hopkins statistic computed during the initial assessment of clustering tendency was $H = 0.828$, confirming a strong, non-random clustering structure. The unsupervised learning algorithm identified three distinct clusters within the sample provided. The clustering solution showed a global average silhouette width of 0.26, indicating an acceptable structure separation. The clusters varied in size, with Cluster 1 containing 23 individuals (average silhouette width = 0.29), Cluster 2 containing 53 (average silhouette width = 0.27), and Cluster 3 containing 24 (average silhouette width = 0.23). While the structure indicated acceptable grouping, a total of 5 patients obtained negative silhouette values in the individual analysis (minimum value = −0.14), suggesting some degree of overlap between the boundaries of the subgroups, which is consistent with the continuous nature of body composition phenotypes.

The t-SNE method confirmed the separation of the three clusters in 2D and 3D spaces (Figure 1). The plot reveals that although the clusters occupied distinct regions of the feature space, transition zones were present together with some outliers, reflecting the moderate silhouette scores.

Variable importance analysis revealed that fluid distribution and lean mass indices were the primary drivers of the cluster separation. TBW index (TBW/m$^2$) was the most discriminatory feature (Mean Decrease Gini = 18.68), followed closely by FFM index (FFM/m$^2$) (18.25) and BCM index (BCM/m$^2$) (17.86).

Interestingly, PhA and FM index (FM/m$^2$) contributed less to the separation of these specific subgroups (Mean Decrease Gini of 13.97 and 13.84 respectively) compared to the hydration and cellular mass indices, suggesting that the identified phenotypes are distinguished primarily by cellular integrity and hydration status rather than adiposity alone.

### 3.2 | Comparison Between Clusters

The body composition characteristics on which the clustering algorithm was based (i.e., height-indexed BIA parameters and PhA) divided by cluster are reported in Table 2, while the general, dietary, and psychopathological characteristics are reported in Table 3. To facilitate the comprehensibility of the results and make direct comparison between clusters easier, the standardized parameters are visualized in Figure 2A.

The cluster analysis identified three distinct body composition phenotypes. Cluster 1 could be described as the "Preserved Body Cell Mass" phenotype, given its significantly higher BMI (15.96 kg/m$^2$), FFM Index, and BCM Index compared to

**TABLE 1** | Descriptive statistics of the entire sample expressed as median [25th—75th percentile] or mean ± standard deviation.

| | **Patients with anorexia nervosa ($n = 100$)** |
|---|---|
| Age (years) | 22.00 [19.00–24.00] |
| Duration of illness (years) | 2.00 [1.00–5.00] |
| BMI (kg/m$^2$) | 15.28 ± 0.99 |
| Body composition parameters | |
| Fat-free mass—FFM (kg) | 36.53 ± 4.69 |
| Fat mass—FM (kg) | 4.34 ± 3.49 |
| Body cell mass—BCM (kg) | 18.11 ± 3.35 |
| Total body water—TBW (L) | 27.30 ± 3.08 |
| Extracellular water—ECW (L) | 13.56 ± 1.88 |
| Phase angle—PhA (°) | 5.36 ± 0.80 |
| 24-h dietary recall | |
| 24-h recall—energy (kcal) | 1090.68 ± 481.80 |
| 24-h recall—protein (g) | 57.72 ± 25.74 |
| 24-h recall—lipids (g) | 39.09 ± 26.03 |
| 24-h recall—carbohydrates (g) | 124.59 ± 60.14 |
| Psychopathology and behaviors | |
| Compensatory exercise (episodes/week) | 6.00 [1.00–9.00] |
| Binge-eating (episodes/week) | 0.00 [0.00–1.00] |
| Purging (episodes/week) | 0.00 [0.00–0.00] |
| BSI global severity index | 1.72 ± 0.76 |
| EDE-Q total score | 3.61 ± 1.50 |
| EDI-2 ineffectiveness | 13.44 ± 7.59 |
| EDI-2 maturity fears | 9.74 ± 5.82 |
| EDI-2 social insecurity | 8.31 ± 4.89 |
| EDI-2 body dissatisfaction | 15.59 ± 6.71 |
| EDI-2 perfectionism | 6.62 ± 4.35 |
| EDI-2 interpersonal distrust | 7.60 ± 4.50 |
| EDI-2 impulse regulation | 7.04 ± 6.77 |
| EDI-2 drive for thinness | 13.81 ± 6.77 |
| EDI-2 bulimia | 2.59 ± 4.40 |
| EDI-2 Interoceptive Awareness | 11.53 ± 7.75 |
| EDI-2 Asceticism | 8.43 ± 4.67 |
| CTQ Total Score | 44.41 ± 12.23 |

Abbreviations: BMI, body mass index; BSI, brief symptom inventory; CTQ, Childhood Trauma Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; EDI-2, eating disorder inventory-2.

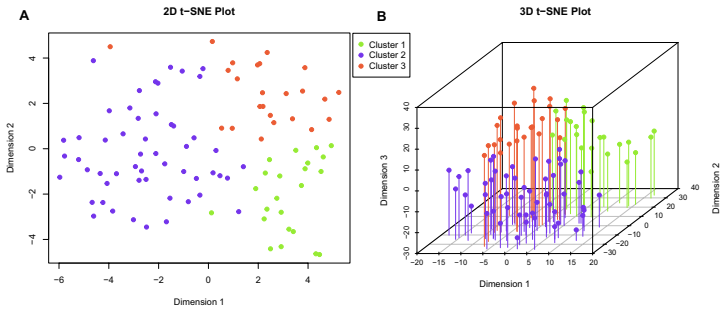


**FIGURE 1** | Visualization of biological phenotypes in Anorexia Nervosa using t-Distributed Stochastic Neighbor Embedding (t-SNE). (A) 2D t-SNE plot illustrating the separation of the three identified clusters based on bioelectrical impedance analysis (BIA) parameters: Cluster 1 (green, "Preserved Body Cell Mass"), Cluster 2 (purple, "Severe Depletion"), and Cluster 3 (orange, "Fluid Redistribution"). (B) 3D t-SNE plot showing the high-dimensional structure and spatial relationship between the three clusters.

**TABLE 2** | Body composition characteristics of the three clusters, expressed as mean ± standard deviation.

| | Cluster 1 "preserved body cell mass" ($n = 23$) | Cluster 2 "severe depletion" ($n = 53$) | Cluster 3 "fluid redistribution" ($n = 24$) | F | Effect size ($\eta_p^2$) |
|---|---|---|---|---|---|
| Body composition parameters | | | | | |
| Fat-free mass—FFM (kg) | 38.04 ± 3.09 | 35.91 ± 3.63 | 36.45 ± 7.25 | 1.68 | 0.033 [0.000–0.100] |
| Fat mass—FM (kg) | 3.93 ± 4.92 | 4.88 ± 2.44 | 3.54 ± 3.77 | 1.45 | 0.029 [0.000–0.092] |
| Body cell mass—BCM (kg) | 20.52 ± 1.72†‡ | 17.84 ± 3.03 | 16.40 ± 3.94 | 11.20*** | 0.188 [0.077–0.295] |
| Total body water—TBW (L) | 28.05 ± 2.52 | 26.37 ± 2.36‡ | 28.62 ± 4.19 | 5.73** | 0.106 [0.021–0.202] |
| Extracellular water—ECW (L) | 12.73 ± 1.60‡ | 13.05 ± 1.35‡ | 15.43 ± 1.92 | 22.98*** | 0.321 [0.195–0.429] |
| Phase angle—PhA (°) | 6.15 ± 1.10†‡ | 5.28 ± 0.42‡ | 4.76 ± 0.41 | 28.31*** | 0.369 [0.242–0.472] |
| Body composition parameters (height-indexed) | | | | | |
| Fat-free mass index (kg/m$^2$) | 14.78 ± 0.43†‡ | 13.20 ± 0.90 | 13.53 ± 2.49 | 10.34*** | 0.176 [0.068–0.282] |
| Fat mass index (kg/m$^2$) | 1.56 ± 2.09 | 1.79 ± 0.88 | 1.33 ± 1.43 | 0.97 | 0.020 [0.000–0.074] |
| Body cell mass index (kg/m$^2$) | 7.99 ± 0.57†‡ | 6.55 ± 0.95 | 6.10 ± 1.44 | 22.66*** | 0.318 [0.192–0.426] |
| Total body water index (L/m$^2$) | 10.92 ± 0.75† | 9.72 ± 0.50‡ | 10.62 ± 1.23 | 22.38*** | 0.316 [0.189–0.423] |
| Extracellular water index (L/m$^2$) | 4.95 ± 0.43‡ | 4.81 ± 0.29‡ | 5.72 ± 0.44 | 52.06*** | 0.518 [0.403–0.605] |

*Note:* Comparisons between groups are reported with *F*-values and the corresponding *p* value expressed as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Post hoc comparisons are reported as follows: † significantly different than Cluster 2, ‡ significantly different than Cluster 3.

both Clusters 2 and 3 (Figure 2A and Table 2); the TBW Index was also significantly higher than in Cluster 2. The remaining two clusters, while showing a similar BMI (15.08 kg/m$^2$ and 15.06 kg/m$^2$ respectively), exhibited significantly different body composition phenotypes. Cluster 2, which represented the "Severe Depletion" phenotype, demonstrated the lowest FFM and TBW Indices (Figure 2A and Table 2), reflecting the most pronounced tissue wasting pattern. Cluster 3, labeled

**TABLE 3** | General, dietary, behavioral and psychometric characteristics of the three clusters, expressed as median [25th–75th percentile] or mean ± standard deviation.

| | Cluster 1 ($n = 23$) | Cluster 2 ($n = 53$) | Cluster 3 ($n = 24$) | $F$ | Effect size ($\eta_p^2$) |
|---|---|---|---|---|---|
| Age (years) | 22 [17.5–22.68] | 22 [19–24] | 22.68 [20.75–26.25] | 1.07 | 0.022 [0.000–0.079] |
| Duration of illness (years) | 3 [1.5–4] | 2 [1–4.75] | 4 [2–7] | 1.00 | 0.020 [0.000–0.076] |
| BMI (kg/m$^2$) | 15.96 ± 0.67†‡ | 15.08 ± 1.02 | 15.06 ± 0.93 | 8.17*** | 0.145 [0.046–0.249] |
| 24-h dietary recall | | | | | |
| 24-h recall—energy (kcal) | 1156.69 ± 489.94 | 1012.80 ± 487.69 | 1200.57 ± 451.29 | 1.21 | 0.025 [0.000–0.084] |
| 24-h recall—protein (g) | 62.54 ± 28.34 | 53.33 ± 23.82 | 62.91 ± 26.77 | 1.30 | 0.026 [0.000–0.087] |
| 24-h recall—lipids (g) | 42.69 ± 21.31 | 34.52 ± 28.34 | 45.80 ± 23.57 | 1.76 | 0.035 [0.000–0.103] |
| 24-h recall—carbohydrates (g) | 133.47 ± 72.00 | 118.10 ± 55.10 | 130.70 ± 60.29 | 0.38 | 0.008 [0.000–0.044] |
| Psychopathology and behaviors | | | | | |
| Compensatory exercise (h/week) | 7 [4–12]‡ | 6 [1–10] | 2.5 [0–7] | 5.64** | 0.105 [0.021–0.201] |
| Binge-eating (episodes/week) | 0 [0–1.5] | 0 [0–1] | 0 [0–0] | 0.31 | 0.006 [0.000–0.039] |
| Purging (episodes/week) | 0 [0–0] | 0 [0–0] | 0 [0–0] | 1.71 | 0.034 [0.000–0.102] |
| BSI global severity index | 2.06 ± 0.90 | 1.52 ± 0.72 | 1.89 ± 0.57 | 1.01 | 0.021 [0.000–0.076] |
| EDE-Q total score | 3.81 ± 1.62 | 3.65 ± 1.53 | 3.31 ± 1.34 | 0.39 | 0.008 [0.000–0.045] |
| EDI-2 ineffectiveness | 13.63 ± 7.92 | 14.49 ± 7.40 | 10.72 ± 7.43 | 1.55 | 0.031 [0.000–0.096] |
| EDI-2 maturity fears | 10.26 ± 5.92 | 10.49 ± 5.81 | 7.39 ± 5.44 | 2.23 | 0.044 [0.000–0.118] |
| EDI-2 social insecurity | 9.21 ± 4.55‡ | 9.21 ± 5.23‡ | 5.22 ± 2.94 | 4.68* | 0.089 [0.012–0.181] |
| EDI-2 body dissatisfaction | 14.32 ± 6.83 | 16.95 ± 6.09 | 13.67 ± 7.58 | 1.99 | 0.040 [0.000–0.111] |
| EDI-2 perfectionism | 6.58 ± 4.25 | 6.74 ± 4.66 | 6.39 ± 3.87 | 0.17 | 0.004 [0.000–0.025] |
| EDI-2 interpersonal distrust | 7.84 ± 4.72 | 8.19 ± 4.52 | 5.94 ± 4.02 | 1.58 | 0.032 [0.000–0.097] |
| EDI-2 impulse regulation | 8.21 ± 6.12‡ | 8.44 ± 7.49‡ | 2.44 ± 2.45 | 5.74** | 0.107 [0.022–0.203] |
| EDI-2 drive for thinness | 13.58 ± 7.37 | 14.19 ± 6.72 | 13.17 ± 6.54 | 0.16 | 0.003 [0.000–0.024] |
| EDI-2 bulimia | 2.84 ± 4.67 | 2.77 ± 4.52 | 1.89 ± 3.98 | 0.34 | 0.007 [0.000–0.041] |
| EDI-2 interoceptive awareness | 10.95 ± 6.79 | 13.23 ± 8.39‡ | 8.06 ± 6.00 | 3.14* | 0.061 [0.001–0.144] |
| EDI-2 asceticism | 10.00 ± 5.80 | 8.72 ± 4.46 | 6.06 ± 2.78 | 2.93 | 0.058 [0.000–0.138] |
| CTQ total score | 47.09 ± 12.58‡ | 45.89 ± 12.53‡ | 38.58 ± 9.50 | 3.23* | 0.063 [0.001–0.146] |

*Note:* Comparisons between groups are reported with $F$-values and the corresponding $p$ value expressed as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Post hoc comparisons are reported as follows: † significantly different than Cluster 2, ‡ significantly different than Cluster 3.
Abbreviations: BMI, body mass index; BSI, brief symptom inventory; CTQ, Childhood Trauma Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; EDI-2, eating disorder inventory-2.

the "Fluid Redistribution" phenotype, was characterized by a significantly elevated ECW Index combined with the lowest BCM Index and PhA (Figure 2A and Table 2), indicating impaired fluid homeostasis and cellular depletion. No significant differences emerged regarding FM across the three phenotypes (Table 2).

Regarding food intake, in the 24-h dietary recall no statistically significant differences emerged between the three clusters (Table 3). Cluster 1 reported the highest frequency of compensatory physical activity, with a median of 7 h per week equivalent to about 1 h per day, significantly higher than Cluster 3 but not Cluster 2 (Table 3).

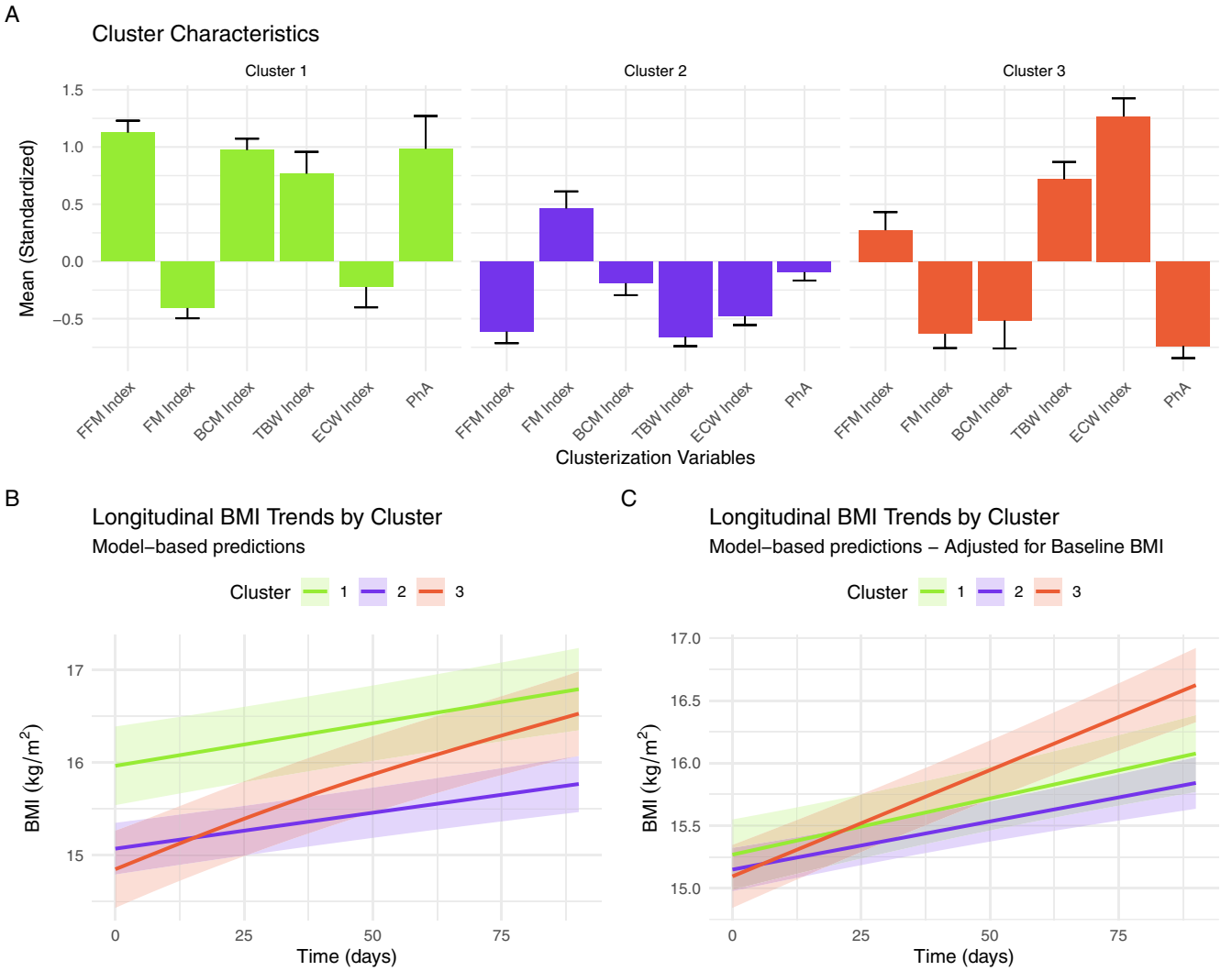


**FIGURE 2** | Cluster profiles and longitudinal weight recovery trajectories. (A) Standardized body composition characteristics by cluster, showing the biological differentiation between "Preserved Body Cell Mass" (Cluster 1), "Severe Depletion" (Cluster 2), and "Fluid Redistribution" (Cluster 3) phenotypes. (B) Model-based longitudinal estimates of BMI recovery over a 3-month follow-up period. (C) Model-based longitudinal estimates of BMI recovery over a 3-month follow-up period, adjusted for baseline BMI. BCM, body cell mass; BMI, body mass index; ECW, extracellular water; FFM, fat-free mass; FM, fat mass; PhA, phase angle; TBW, total body water.

Regarding psychopathological features, no significant differences emerged between clusters in core ED psychopathology, as evidenced by similar EDE-Q scores and EDI-2 drive for thinness, body dissatisfaction, and bulimia (Table 3). However, scores related to traits associated with AN measured by the EDI-2 showed that Clusters 1 and 2 had higher levels of social insecurity and impulse dysregulation compared to Cluster 3; additionally, Cluster 2 exhibited worse interoceptive awareness (Table 3).

Exposure to childhood abuse and neglect (trauma) was reported by 13 (56.5%) patients in Cluster 1, 26 (49.1%) in Cluster 2, and 5 (20.8%) in Cluster 3. Fisher's exact test confirmed that the differences between these proportions were statistically significant ($p = 0.021$), with a lower percentage in Cluster 3 compared to the other two ($p = 0.025$ for both post hoc tests). These results were consistent with CTQ scores, which confirmed that Cluster 3 had a lower exposure to childhood traumatic experiences compared to the other clusters (Table 3).

No statistically significant differences were found in the proportion of patients with the Binge-eating/purging subtype between clusters ($p = 0.690$), with 9 (39.1%) in Cluster 1, 25 (47.2%) in Cluster 2, and 9 (37.5%) in Cluster 3.

### 3.3 | Weight Recovery at 3 Months

At the 3-month dietary follow-up from baseline, 32 (32%) patients had achieved a recovery compatible with a moderate early response, and 17 (17%) with a rapid early response. Overall, patients reached a mean BMI of $16.14 \pm 1.39$, but there were significant differences between clusters. In particular, the "Preserved Body Cell Mass" phenotype (Cluster 1) reached a mean BMI of $16.74 \pm 1.30$, the "Severe Depletion" cluster (Cluster 2) a BMI of $15.81 \pm 1.34$, and the "Fluid Redistribution" cluster a BMI of $16.30 \pm 1.42$, with significant differences between Cluster 1 and Cluster 2 ($p < 0.05$ in the post hoc tests, with overall $F = 3.97$,

**TABLE 4** | Results of the Generalized Additive Mixed Models (GAMMs). For each model, the estimates of the parametric coefficients are reported, along with the statistics and *p* values of all components.

| **Model 1—Cluster 1 as reference cluster** | | | |
|---|---|---|---|
| Effect Size—Adj. $R^2 = 0.169$ | | | |
| Parametric coefficients | | | |
| | Estimate | *t* value | *p* |
| Intercept | 16.29 | 78.94 | **< 0.001** |
| Cluster 2 | −0.95 | −3.82 | **< 0.001** |
| Cluster 3 | −0.73 | −2.53 | **0.012** |
| Smooth terms | | | |
| | EDF | *F* statistic | *p* |
| s(Time) | 1.00 | 27.21 | **< 0.001** |
| s(Time) * Cluster 2 | 1.00 | 0.44 | 0.507 |
| s(Time) * Cluster 3 | 1.63 | 8.17 | **< 0.001** |
| **Model 2—Cluster 2 as reference cluster** | | | |
| Effect size—Adj. $R^2 = 0.169$ | | | |
| Parametric coefficients | | | |
| | Estimate | *t* value | *p* |
| Intercept | 15.35 | 112.46 | **< 0.001** |
| Cluster 1 | 0.95 | 3.82 | **< 0.001** |
| Cluster 3 | 0.21 | 0.87 | 0.383 |
| Smooth terms | | | |
| | EDF | *F* statistic | *p* |
| s(Time) | 1.00 | 38.30 | **< 0.001** |
| s(Time) * Cluster 1 | 1.00 | 0.44 | 0.507 |
| s(Time) * Cluster 3 | 1.63 | 14.88 | **< 0.001** |
| **Model 3—Cluster 3 as reference cluster** | | | |
| Effect size—Adj. $R^2 = 0.169$ | | | |
| Parametric coefficients | | | |
| | Estimate | *t* value | *p* |
| Intercept | 15.5614 | 76.922 | **< 0.001** |
| Cluster 1 | 0.7324 | 2.535 | **0.011** |
| Cluster 2 | −0.2126 | −0.871 | 0.384 |
| Smooth terms | | | |
| | EDF | *F* statistic | *p* |
| s(Time) | 1.01 | 119.56 | **< 0.001** |
| s(Time) * Cluster 1 | 1.00 | 15.37 | **< 0.001** |
| s(Time) * Cluster 2 | 1.00 | 27.16 | **< 0.001** |
| **Model 4—Adjusted for baseline BMI, Cluster 1 as reference cluster** | | | |
| Effect size—Adj. $R^2 = 0.564$ | | | |
| Parametric coefficients | | | |
| | Estimate | *t* value | *p* |
| Intercept | 2.19 | 2.14 | **0.033** |
| Cluster 2 | −0.17 | −1.07 | 0.284 |
| Cluster 3 | 0.11 | 0.64 | 0.525 |
| Baseline BMI | 0.88 | 13.88 | **< 0.001** |
| Smooth terms | | | |
| | EDF | *F* statistic | *p* |
| s(Time) | 1.00 | 28.03 | **< 0.001** |
| s(Time) * Cluster 2 | 1.00 | 0.39 | 0.535 |
| s(Time) * Cluster 3 | 1.00 | 11.41 | **< 0.001** |

*Note:* For smooth terms, the Effective Degrees of Freedom (EDF) are also reported. Models 1, 2, and 3 represent variations of the same model, in which a different cluster was included each time as the reference cluster to allow post hoc comparisons between each cluster in relation to the trend over time. Model 4 represents a variation of Model 1, adjusted for baseline BMI. Bold values are significance values.

$p = 0.022$). Month-by-month values for each cluster are reported in Table S2.

The nonlinear mixed models confirmed that the improvement over time was statistically significant in all clusters ($p < 0.001$ in all clusters). The post hoc tests performed, reported in Table 4 (Models 1, 2, and 3), confirmed a similar trend over time between Clusters 1 and 2 (Model 1 in Table 4). In contrast, Cluster 3 (the "Fluid Redistribution" phenotype) recovered significantly more weight during the observation period compared to the other two phenotypes (Model 3 in Table 4), as visible from the model-based longitudinal estimates illustrated in Figure 2B. Adjusting the model for baseline BMI confirmed these differences (Model 4 in Table 4); Figure 2C illustrates model-based longitudinal trends simulating similar baseline BMI among clusters.

## 4 | Discussion

The present study aimed to integrate the current BMI-based classification, addressing the limitations of a single-parameter model by introducing a novel ML clustering approach based on

BIA parameters. Importantly, the critique of BMI in this work is directed at its use as a static baseline staging parameter, which fails to capture somatic heterogeneity and lacks prognostic utility, rather than its role as a standardized longitudinal metric for tracking weight recovery.

Indeed, in a rather homogeneous sample in terms of BMI, this technique was able to highlight three very different clusters of patients with AN, with respect to both body composition and psychopathology, highlighting substantial heterogeneity in nutritional and cellular impairment. It is important to note that these clusters were not fully characterized by BMI, as only the first cluster significantly differed in BMI compared with the second and third clusters, which instead exhibited virtually identical baseline BMI values (15.08 vs. 15.06 kg/m (Russell 2020)). This distinct separation between Clusters 2 and 3, despite equivalent baseline weight severity, indicates that the clustering solution was not merely an artifact of baseline BMI or overall somatic severity, but rather captured distinct underlying bioelectrical phenotypes. Moreover, no significant differences were found regarding nutritional intake at the 24 h dietary recall, further confirming that the highlighted differences were not to be attributed simply to different caloric intakes.

The first cluster, termed the "Preserved Body Cell Mass" phenotype, was characterized by relatively preserved BCM and FFM indices, suggesting maintained cellular integrity and lean tissue despite an underweight condition. This cluster also showed higher PhA values, closer to those reported in the literature for individuals in good health, supporting the interpretation of a less compromised cellular status. This could represent an early-stage AN phenotype, where somatic reserves are relatively spared despite low weight; conversely, Clusters 2 and 3 appear to represent two divergent paths of severe malnutrition. The "Severe Depletion" phenotype (Cluster 2) exhibited a profile of global tissue wasting, with the lowest FFM and TBW indices, indicating a "chronic marasmic" state where the body had exhausted its reserves. On the contrary, the "Fluid Redistribution" phenotype (Cluster 3) exhibited a distinct pattern, characterized by increased ECW together with reduced BCM and PhA, indicating impaired cellular integrity and disrupted homeostasis rather than simple weight loss. Low PhA is a well-documented marker of impaired cell membrane integrity, and the presence of high ECW in this group may potentially correspond to altered fluid distribution across compartments due to the "leakage" of intracellular fluid into the extracellular space, a phenomenon often seen in acute states (Zheng et al. 2023).

Considering the follow-up data, approximately half of the sample (49%) achieved partial weight restoration that could be considered at least moderate, consistent with the limited duration of treatment (3 months). These values are largely comparable to those highlighted in the study by Wade et al., where in a similar setting 48% of a sample of patients with AN achieved partial weight restoration after the first 13 treatment sessions (Wade et al. 2021). Moreover, the comparisons between clusters showed a kind of "paradoxical effect", in which the greatest gains were observed in the third cluster, which displayed some of the worst BIA indices if interpreted individually, further supporting the need for a holistic view of biological features. This finding can be explained in several ways. On the one hand, the fluid redistribution features highlighted by BIA-derived body composition might indicate a more acute state of wasting, rather than a chronic adaptation to starvation.

While purely speculative, it could be hypothesized that BIA data in Cluster 2 align with a profile of chronic undernutrition, where a tendency toward dehydration emerges, whereas Cluster 3 might reflect a more recent state of semi-starvation accompanied by fluid accumulation and altered distribution (Davies and Cole 1995). It could be argued that the rapid early weight trajectory observed in Cluster 3 might partially reflect the stabilization of initial fluid shifts, considering the baseline fluid redistribution of this phenotype. However, previous studies reported that during early nutritional rehabilitation in AN, extracellular water expansion and edema commonly occur in the first weeks of refeeding and usually stabilize thereafter (Vaisman et al. 1988). Thus, the fact that the accelerated weight trajectory in Cluster 3 was maintained over a 3-month observational period may suggest genuine tissue restoration, rather than mere fluid retention. A less chronologically entrenched state in Cluster 3 might remain less metabolically entrenched, compared to hypothesized chronic adaptations in Cluster 2, thereby potentially facilitating a more robust and dynamic physical response to nutritional rehabilitation, though these distinct biological mechanisms were not directly measured and require further empirical confirmation. One of the mechanisms underlying this chronic adaptation could be leptin-based, and in fact hypoleptinemia is considered one of the key factors behind the entrapment in AN (Cassioli et al. 2025; Hebebrand et al. 2024).

On the other hand, the psychopathological characterization of the three clusters sheds light on other important possible underlying mechanisms. The two clusters that showed less weight recovery (Cluster 1 and 2) were those with greater exposure to childhood traumatic experiences, with a proportion of patients reporting childhood trauma that was more than double that observed in Cluster 3. Furthermore, Cluster 3 showed CTQ values ($CTQ_{Total\ Score} = 38.58$) overlapping with those of community samples ($CTQ_{Total\ Score} = 38.78$) (MacDonald et al. 2016) and healthy control populations ($CTQ_{Total\ Score} = 35.35$) (Cassioli et al. 2021), while Cluster 1 and 2 had scores ($CTQ_{Total\ Score} = 45.89–47.09$) similar to those highlighted in clinical populations exposed to childhood traumatic experiences (MacDonald et al. 2016; Cassioli et al. 2021). In addition, the other between-cluster psychopathological differences, namely higher levels of social insecurity and impulse regulation, are in line with common traits seen in maltreated individuals (Rossi, Cassioli, Dani, et al. 2024). Therefore, these findings are in line with the existence of a subpopulation of patients with a history of childhood abuse (i.e., the "maltreated echophenotype"), showing a different response to treatment, in particular a more resistant or slower weight recovery trajectory in response to standard treatments highlighted in previous studies (Rossi, Cassioli, Cecci, et al. 2024; Cassioli et al. 2021; Castellini et al. 2018). Although the cross-sectional nature of baseline assessments precludes inferring a causal pathway between early life stress and specific body composition phenotypes, several speculative mechanisms may explain this phenomenon. First, it is plausible that the numerous comorbid dysfunctional traits associated with a history of childhood maltreatment led to greater difficulties in treatment adherence and adhering to medical and dietary recommendations. For

example, higher levels of impulsivity, emotional dysregulation, and dissociation (Rossi, Cassioli, Cecci, et al. 2024) could more easily trigger losses of control over food during the nutritional rehabilitation phase, leading the patient to greater caution and persistence of food restriction. Similarly, the lower levels of interoceptive awareness that characterize the maltreated ecophenotype of AN (Rossi, Cassioli, Dani, et al. 2024; Monteleone et al. 2019) could lead to increased levels of body concerns and body dysmorphia during weight recovery, given the inability to rely on somatic markers to reassure oneself.

This study presents several key strengths, including the adoption of a data-driven approach, specifically ML-based clustering of biological data, and the further characterization of the resulting clusters from a psychopathological perspective and in terms of initial weight restoration using longitudinal data. Regardless of the actual underlying mechanisms, the results suggest the potential utility of BIA parameters in the staging of AN, as their ability to stratify patients into clusters did not merely represent "better" or "worse" conditions, but rather different morpho-functional patterns with distinct illness trajectories specifically regarding early weight recovery kinetics. While these findings do not imply that clusters differ in total clinical treatment response or psychopathological remission, they demonstrate that baseline body composition profiles are significantly coupled with the rate and pattern of initial physical rehabilitation. This provides exploratory support against relying solely on a purely BMI-centric staging model and suggests that individual biological phenotypes may influence how a patient initially responds to nutritional restoration. By adhering to standardized ESPEN guidelines for BIA assessment, the impact of transient intake-related fluctuations was minimized in the present study. Furthermore, the 3-month follow-up period allowed the observation of stable weight recovery trajectories, extending beyond the acute fluid compartment shifts typically observed in the early refeeding phase. Together, these methodological strengths suggest that the identified clusters reflect stable phenotypes rather than state-dependent variations in hydration or recent dietary intake, supporting the potential value of BIA in future precision-staging research in AN. As these are preliminary results, several limitations should be acknowledged. The single-center design, modest sample size, inclusion of only female participants, and use of a restricted set of six BIA-derived parameters limit the generalizability of the results. While although strict ESPEN standardization protocols were followed and raw parameters like PhA were included, other BIA indices still rely on population-derived predictive equations, which assume constant tissue hydration (an assumption that can be strained in severely underweight states). Nevertheless, a methodological strength of this study is that it did not rely on absolute quantitative thresholds of individual derived measures. By employing an unsupervised ML framework, the analysis evaluated relative multivariable patterns across compartments, mitigating potential absolute estimation bias in single equations. The URF-derived cluster solution, with its global average silhouette width of 0.26, should be considered exploratory and requires external replication in larger, independent samples. While a silhouette width of 0.20–0.30 indicates modest geometric separation, this can be expected when modeling continuous biological phenotypes like BIA parameters (Hennig 2015). Crucially, a high Hopkins statistic confirmed a strong clustering tendency, rejecting the null hypothesis of a uniform, non-clustered spatial distribution. However, while the Hopkins statistic demonstrates that the data exhibit a significant tendency to cluster, the internal stability and reproducibility of this specific three-cluster solution was not formally evaluated due to sample size constraints. Most importantly, the clinical relevance of these clusters is supported by their external-variable (criterion-related) characterization: despite overlapping baseline BMIs, these phenotypes differed significantly in childhood trauma exposure and early weight-recovery trajectories, reflecting distinct morpho-functional states within this cohort. However, because baseline parameters, including childhood trauma, were assessed cross-sectionally, these associations cannot clarify developmental pathways or causal mechanisms linking early life stress to body composition. Given the exploratory nature of the secondary analyses, corrections for multiple testing were not applied across the broader set of comparisons. Because of the limited sample size and the fact that many of these measures exhibit substantial collinearity, standard multiplicity adjustments would be overly conservative, markedly increasing the risk of Type II error. However, there is some risk of increasing the rate of Type I errors. In addition, no longitudinal measures of eating-disorder psychopathology were collected. Furthermore, raw bioelectrical metrics (resistance, reactance, height-normalized components, and Bioelectrical Impedance Vector Analysis parameters) as well as biochemical markers of hydration status (e.g., serum electrolytes, albumin, and renal function indices) were not recorded for the present study. While clinical examination confirmed the absence of overt peripheral edema, the lack of systemic laboratory hydration biomarkers limits direct physiological validation of the 'Fluid Redistribution' phenotype interpretation. Future prospective studies should explicitly incorporate raw electrical vectors, BIVA modeling, and laboratory hydration profiling to further validate these findings. Because the outcome of the present study was early weight restoration, follow-up was limited to 3 months; this timeframe was considered insufficient to capture meaningful changes in psychopathology. Furthermore, 12 participants were lost to follow-up and excluded from the longitudinal trajectory analyses. Although baseline characteristics did not differ significantly between retained participants and those lost to follow-up, these comparisons cannot establish that missingness was at random or exclude attrition related to unmeasured or time-varying clinical factors. Because participants who discontinued treatment provided observations only during the early treatment phase, their inclusion in the GAMMs would have informed early but not later trajectory segments, and estimates of full follow-up trajectories could have been sensitive to assumptions regarding the missing-data mechanism. Accordingly, the longitudinal findings should be interpreted as describing weight-recovery trajectories among participants who remained under observation throughout the 3-month period. Finally, while the biological clusters demonstrated significant associations with longitudinal weight trajectories, potential mediators including treatment-related process variables (e.g., adherence, intervention intensity, supplement compliance, meal completion) as well as other biological and psychological factors (e.g., leptin levels and trauma-related psychopathology) were not systematically tracked, and their mediating role warrants further investigation in future research.

## 4.1 | Conclusion and Clinical Implications

These results highlight the utility of exploring clinical refinements in how nutritional risk and recovery potential are evaluated in AN, moving from a BMI-centric approach to a future staging process aligned with the biopsychosocial model of psychiatric disorders. In this context, BIA could represent a highly feasible tool for routine ED units. Unlike DEXA, which requires specialized radiological facilities, significant financial investment, and exposure to low-level radiation, the BIA equipment used in this study is portable, non-invasive, and relatively low-cost (typically ranging from €4000 to €7000) (Dupertuis et al. 2025). The assessment itself is extremely low-burden for the patient, requiring only 5–10 min of supine rest for fluid stabilization and less than 60 s for the actual data collection. Given its rapid execution and absence of radiation, BIA can be repeated frequently to monitor nutritional rehabilitation trajectories in real time, making it a feasible tool in the field of personalized care for AN. Furthermore, the integration of BIA data with relevant anamnestic factors, such as a history of childhood abuse and neglect, and biological factors possibly associated with poor weight recovery, such as alterations in leptin and ghrelin, would represent a further step toward a staging process aligned with the modern model of precision psychiatry. Preliminary data already point to a possible benefit from the integration of trauma-focused psychotherapeutic approaches in the treatment pathway of particular subgroups of patients with AN (Rossi, Cassioli, Dani, et al. 2024), and it is conceivable that a similar approach could be implemented in the context of nutritional rehabilitation, with interventions targeted at specific subpopulations.

### Author Contributions

**Emanuele Cassioli:** conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, visualization, project administration, resources, writing – original draft, writing – review and editing. **Gaia Maiolini:** data curation, investigation, writing – original draft, writing – review and editing. **Eleonora D'Areglia:** data curation, investigation, writing – original draft, writing – review and editing. **Livio Tarchi:** conceptualization, data curation, methodology, project administration, supervision, validation, writing – original draft, writing – review and editing. **Eleonora Rossi:** conceptualization, data curation, methodology, project administration, supervision, validation, writing – original draft, writing – review and editing. **Veronica Ceccarelli:** investigation, writing – review and editing. **Cristiano Dani:** data curation, investigation, writing – review and editing. **Luca Zompa:** data curation, writing – review and editing. **Chiara Ranieri:** data curation, writing – review and editing. **Enrico Lodovici:** data curation, writing – review and editing. **Anita Nannoni:** supervision, writing – review and editing. **Valdo Ricca:** project administration, resources, supervision, validation, writing – review and editing. **Giovanni Castellini:** conceptualization, project administration, resources, supervision, validation, writing – review and editing.

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Descriptive statistics, expressed as mean ± standard deviation or median [interquartile range], for both the final study cohort and individuals who were lost to follow-up or who dropped out following initial assessment, alongside adjusted comparative analyses between the two groups. **Table S2:** Body Mass Index (BMI) over time, divided by cluster. Values are expressed as mean ± standard deviation.