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Article

Biomarkers for Phenotypic Classification of Patients with Acute Psychiatric Symptoms: The Relevance of White Matter Hyperintensities

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Abstract

Background/Objectives: The investigation of biomarkers capable of identifying subgroups of psychiatric patients based on a combination of clinical and neurobiological features, such as white matter hyperintensities (WMH), will enable more accurate medical practice, with a better prediction of clinical presentation, progression, and response to treatment. The aim of this study was to investigate whether patients with acute psychiatric symptoms could be grouped according to clinical and neurobiological features. **Methods**: A k-means cluster analysis of 90 acute psychiatric inpatients, aged 45 to 75 years, who met criteria for schizophrenia, bipolar disorder, and major depressive disorder was performed. Multidimensional clinical and neuroimagological data were included in the analysis. Validity of the clusters was tested by re-clustering the sample and comparing the silhouette coefficient. **Results**: The cluster analysis extracted three clinical phenotypes that can be identified based on the burden of WMH. A "vascular-cognitive" phenotype (cluster 1, n=13), a "low vascular-psychiatric" phenotype (cluster 2, n=58), and a "vascular-depressive/apathy" phenotype (cluster 3, n=19). The silhouette coefficient was higher in the clusters including the WMH variable, reflecting a structuring effect on the clusters. **Conclusions**: The cluster analysis extracted subgroups of subjects that can be distinguished by WMH burden, cognitive performance, and psychiatric symptoms.

Keywords: white matter hyperintensities; cerebral small vessels disease; neuropsychiatric symptoms; cognitive impairment; vascular risk factors

1. Introduction

Despite the consensus that the classification of psychiatric diseases should be based on etiological factors, most classifications are syndromic, as the pathophysiology of mental illnesses remains elusive. Therefore, neurobiological criteria cannot be used, unlike for other medical conditions. (Goldberg, 2015; Jablensky, 2016)

The psychiatric illnesses have a categorical classification system based on the identification of clinical syndromes that aggregate phenotypic characteristics. These are superficial and not "natural" features of the disease, resulting in lack of diagnostic stability and validity.(Saraiva, 2014)

There is an urgent need to develop useful biomarkers capable of identifying subgroups of patients with similar characteristics, based on a combination of symptoms, neurobiological features and other risk factors. Biomarkers will enable more accurate medical practice, as they will allow

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earlier diagnosis, better prediction of clinical progression, and better prediction of response to treatment. (Giegling et al., 2017a)

Most psychiatric patients present with functional and structural brain alterations, both transdiagnostic and disorder specific. (Giegling et al., 2017b; Schmitt et al., 2017) Evidence shows that changes in neuroanatomical measures account for 40% of variance in clinical outcome.(Scarpazza et al., 2020)

Elucidating how distinct biological factors co-occur in subgroups of patients with major psychiatric conditions will contribute to disclosing pathophysiology. It is likely that specific features occurring more frequently together may share common pathways. However, the co-occurrence of clinical and neurobiological factors has rarely been addressed in clinical practice.

The aim of this study was to test whether patients with major psychiatric syndromes can be classified into meaningful subgroups according to clinical and neurobiological features. We investigated factors accessible to daily clinical practice so that the results of this research can be easily applied.

Hereafter, these data will allow the implement of targeted interventions for prevention and treatment of these disorders.

2. Methods

2.1. Participants

The investigators performed a cross-sectional study of patients consecutively admitted on the acute psychiatric ward of a University Hospital (Coimbra Local Health Unit) from October 2022 to October 2024, aged 45 to 75 years, who met the criteria for schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5). The exclusion criteria are presented in appendix 1.

The ethics committee of the University Hospital (Coimbra Local Health Unit) approved all the procedures used in this study, including the method of obtaining consent, in accordance with the Declaration of Helsinki. Study protocols and rationale were explained to the participants and all provided written informed consent.

2.2. Measures

The entire assessment was carried out by experienced psychiatrists. Information regarding sociodemographic data, medical and psychiatric history, and family history of psychiatric illnesses was collected throught a questionnaire.

2.3. Psychiatric Symptoms Assessment

All patients were evaluated with the Structured Clinical Interview for DSM-5 —Clinician Version (SCID-5-CV) for psychiatric diagnosis during the acute phase of decompensation, by two experienced psychiatrists. The Neuropsychiatric Inventory (NPI) 12-item version, was used to operationalize the psychiatric symptoms. As the patient was evaluated during the hospitalization, the interviewer assessed the NPI items based in direct clinical observation. (Cummings, 2020; Cummings et al., 1994; Ferreira et al., 2015)

The NPI assess 12 symptoms domains: delusions, hallucinations, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, and sleeping and eating disorders. The scoring procedure is described elsewhere (Cummings et al., 1994).

Suicide behavior was accessed with the Suicide Behaviors Questionnaire-Revised (SBQ-R), which evaluates lifetime suicide ideation and/or suicide attempt, frequency of suicide ideation over the twelve months, threat of suicide attempt, self-reported likelihood of suicidal behavior in the future. (Campos & Holden, 2019; Osman et al., 2001)

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The functionality was assessed with the Global assessment of functioning (GAF) scale, consisting of a numerical scale ranging 100 (extremely high functioning) to 1 (severely impaired), that assesses the impact of mental illness on an individual's daily life impairment associated with psychiatric symptoms. (Aas, 2011)

2.4. Cognitive Assessment

Cognitive assessment occurred after clinical stability was achieved. Patients underwent the Mini Mental Status Examination (MMSE) (Santana et al., 2016) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). MoCA total scores were adjusted for educational level by adding an extra point to the total score for those individuals with less than or equal to 12 years of education.(Freitas et al., 2010)

For motor speed assessment patients underwent Finger tapping test (FFT) using the TappingPro® mobile app. (Axelrod et al., 2014; Barut et al., 2013; Navarro-López et al., 2024) The score is the average number of taps in 10 seconds, with the dominant hand, across the three trials.(Arnold et al., 2005)

2.5. Neuroimaging and WMH Assessment

The neuroradiologic assessment was made by a team of two neuroradiologists that independently classified the images, blind to the diagnosis. Differences in score attribution were resolved by discussion. Neuroimaging protocol is described in appendix 2.

WMH burden assessment was made with Fazekas scale and Modified Scheltens rating scale (MSRS). Fazekas scale attributes a grade to periventricular white matter and deep white matter depending on the size and confluence of lesions.(Fazekas et al., 1987)

The MSRS classifies subregions separately (periventricular WMH: occipital caps, frontal caps and lateral ventricles bands; deep WMH: frontal, parietal, occipital and temporal lesions).(Scheltens et al., 1993)

2.6. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 29.0. Descriptive analysis was used to determine clinical characteristics of the participants.

Two cluster analysis methods were performed to identify subgroups of patients. The hierarchical clustering method was first used to define the optimal number of clusters. All variables were standardized to Z scores. Ward's method was employed to minimize the variance in each group. The examination of the agglomeration schedule and the dendrogram confirmed a distribution among the three subgroups of patients (appendix 3).(Allen & Goldstein, 2013)

To distribute the subjects among the clusters the k-means clustering method was used, fixing the number of clusters at three, as determined in the hierarchical analysis.(Steinley, 2006) For both clustering methods, squared Euclidian distance was used.(Everitt et al., 2011)

The variables included in the cluster analysis were: age, sex, academic qualifications, smoking, history of hypertension, diabetes, and dyslipidemia, body mass index (BMI), medication status, age of psychiatric illness onset, number of hospitalizations in psychiatric ward, family history of psychiatric diseases in first and second degree relatives (dementia before and after 65, psychotic spectrum disorders, mood/affective spectrum disorders, suicide), physical activity, GAF score, NPI-12 score, MoCA and MMSE scores, FTT, SPES, SBQ-R, Fazekas grade and MSRS total score and sub-scores.

Cluster differences were analyzed with chi-square analysis for categoric variables, ANOVA for continuous normality distributed variables and Kruskal-Wallis analysis for nonnormal continuous variables. For multiple comparisons between clusters, Fisher's LSD statistics and ANOVA on ranks method were interpreted for continuous variables with normal and non-normal distribution, respectively.

The level of significance (alpha) was 0.5. Variables which showed a significant difference ($p<0.05$) between the clusters were incorporated in the cluster in which they were more prevalent.

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Tho test for consistency of the clusters, we re-clustered the sample without the WMH variable and compared the silhouette coefficient of each clustering.

Given the high number of comparations between variables across the clusters, a multiple comparison error control at the False discovery rate (FDR) was applied to limit the expected proportion of false positives among significant outcomes, therefore increasing robustness of the analysis. Within each domain, the p-values were adjusted using the Benjamini–Hochberg (BH) method.

3. Results

3.1. Baseline Characteristics

A total of 128 patients were recruited, but only 90 patients were included in the final sample. Thirty-five subjects were excluded due to: episodes of *delirium* during hospitalization, diagnosis of Parkinson's disease, signs of stroke on MRI, and signs of trauma on MRI. Eight patients declined to participate in the study, corresponding to a nonresponse rate of 8.16%.

The mean age of the sample was 59.8 (SD 7.7) years, ranging from 45 to 75 years. The sample was composed of 28.9% males and 71.1% females. The most frequent psychiatric diagnosis was BP (41.1%), followed by MDD (31.1%) and Schizophrenia (27.8%).

Cluster analysis identified 3 clusters (appendix 3) and assigned 13 individuals to cluster 1, 58 to cluster 2, and 19 to cluster 3 (Appendix A.4 – Tables A1–A7).

Figures 1 and 2 present a radar chart and a diagram illustrating the significant differences between variables in the three clusters. The chart provides a multidimensional view of the differences between the clusters and the discriminative power of neurobiological markers, particularly vascular risk factors and neuroimaging markers. The chart displays standardized z-scores. Positive z-scores indicate values above the sample mean, while negative scores indicate values below the mean.

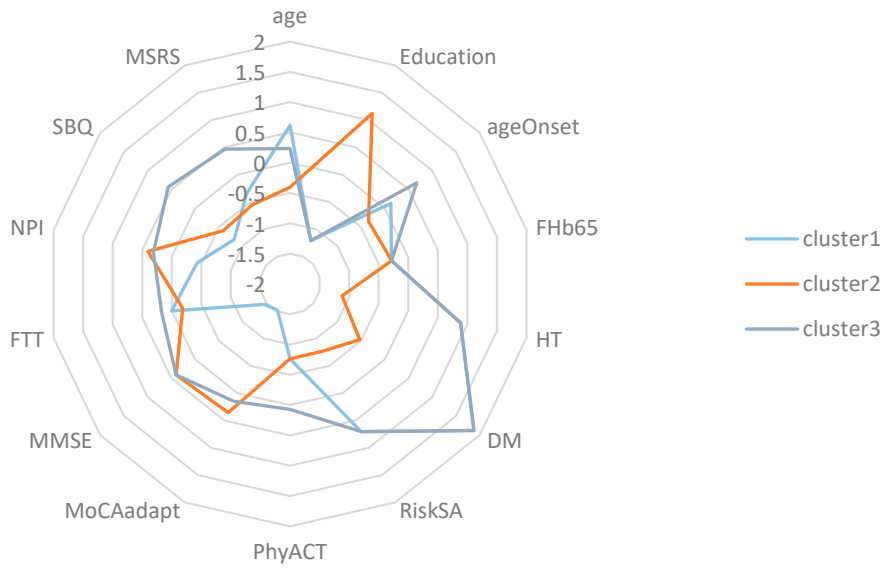

Figure 1. Radar chart of z-scores of variables with significant differences between clusters. HT – hypertension, DM – Diabetes Mellitus, RiskSA – Sleep apnea and risk of sleep apnea, PhyAct – physical activity, MoCA - Montreal Cognitive Assessment, PsyOnset – Age of psychiatric illness onset, FH - Family history, MMSE - Mini-Mental State Examination, FTT – Finger tapping test, NPI - Neuropsychiatric inventory, SBQ-R - Suicide Behaviors Questionnaire, MSRS – Modified Scheltens Rating scale.

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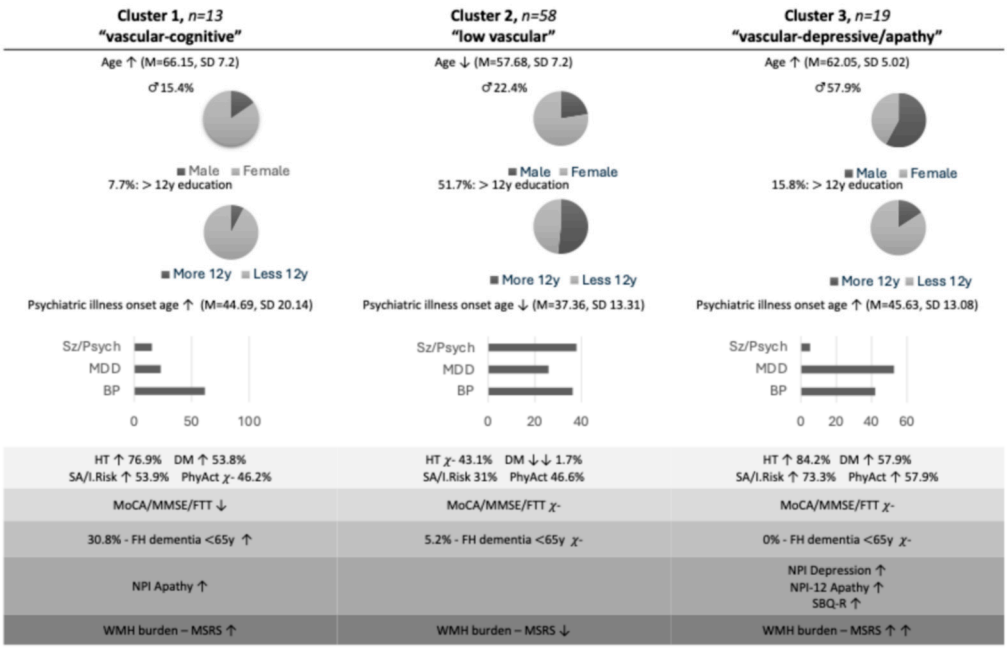

Figure 2. Key significant differences between clusters. Sz/Psych – Schizophrenia, MDD - Major Depressive disorder, BP - Bipolar disorder, HT – hypertension, DM – Diabetes Mellitus, MoCA - Montreal Cognitive Assessment, MMSE - Mini-Mental State Examination, FTT – Finger tapping test, NPI - Neuropsychiatric inventory 12 items, SBQ-R - Suicide Behaviors Questionnaire, WMH – white matter hyperintensities, MSRS – Modified Scheltens Rating scale.

3.2. Cluster 1

3.2.1. Sociodemographic Profile

Cluster 1 aggregates the oldest patients (66.15, SD=7.20), with the lowest level of education (69.2% with 4 years of schooling), and with the highest proportion of women (84.6%).

3.2.2. Medical History

Concerning medical history, these patients present a high prevalence of hypertension (76.9%) and diabetes (53.8%), SA/increased risk of SA (53.9%), a high prevalence of sedentary behaviors (53.8%), and a frequent use of cardiovascular medication.

3.2.3. Psychiatric Profile

This cluster has the highest proportion of patients with BP (61.5%), late onset of psychiatric disease (44.69 years, SD=20.14), and the highest proportion of family history of early onset dementia (before 65 years). Cluster 1 also has higher apathy score (NPI), but not as expressive as in cluster 3.

3.2.4. Cognitive Profile and Psychomotricity

These patients present the worse cognitive performance, presenting with the lowest scores on the MMSE (22.92 years, SD=3.12) and MoCA (13.07 years, SD=3.94), with significant deficits in the domains of attention, executive functions and abstraction.

This cluster has also has the lowest psychomotor velocity (FTT: 40.61 taps, SD=8.69).

3.2.5. White Matter Hyperintensities

This cluster presents a moderate total score in the MSRS, with no significant difference compared to cluster 2 in the total score, but with higher in some sub-regions (occipital deep and temporal deep).

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3.3. Cluster 2

3.3.1. Sociodemographic Profile

These are the youngest patients (57.68 years, SD=7.20), with the highest level of education (>12 years of education: 51.7%).

3.3.2. Medical History

Patients in Cluster 2 have a low prevalence of vascular risk factors (HT: 43.1%, diabetes: 1.7%), a low prevalence of SA/increased risk of SA (31%), and a high prevalence of sedentary behaviors (53.4%).

3.3.3. Psychiatric Profile

This cluster presents an equilibrated distribution between schizophrenia (37.9%), BP (36.2%) and MDD (25.9%). These patients have the earliest onset of psychiatric disease (37.36, SD=13.31).

3.3.4. Cognitive Profile and Psychomotricity

Patients in cluster 2 present the best cognitive performance (MoCAa: 22.51, SD=3.47; MMSE: 27.60, SD=2.00), with preserved executive functions. These patients also present the highest psychomotor velocity (FTT: 50.43 taps, SD=9.93).

3.3.5. White Matter Hyperintensities

These patients have the lowest MSRS score and no significative differences in Fazekas scale.

3.4. Cluster 3

3.4.1. Sociodemographic Profile

This cluster has an intermediate mean age (62.05 years, SD=5.02), low-medium level of education, and the highest proportion of men (57.9%).

3.4.2. Medical History

These patients have the highest prevalence of HT (84.2%) and diabetes (57.9%), higher risk of SA/increased risk of SA (73.3%) but are the most physically active.

3.4.3. Psychiatric Profile

Cluster 3 has the highest proportion of patients with MDD (52.6%) and late onset of psychiatric illness (45.63 years, SD=13.08).

3.4.4. Cognitive Profile and Psychomotricity

Cognitive performance and psychomotor velocity are similar in cluster 2 (MoCAa: 22.57, SD=2.91), but the patients have higher scores in depression and apathy domains (NPI), as well as a greater suicide risk (SBQ-R: 9.73, SD=4.91).

3.4.5. White Matter Hyperintensities

This cluster has a higher burden of WMH assessed by MSRS, particularly of deep parietal lesions.

3.5. False Discovery Rate Correction

After False discovery rate correction by domains (sociodemographic data, psychiatric history, medical history, cognition, psychopathology and WMH burden),

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MoCA total and subtests, psychomotor speed, WMH burden, and medical history variables remained informative for phenotypic stratification. The variables physical activity, and age of onset of psychiatric illness had a modest effect since did not withstand adjustment (Appendix A.4, Table A8).

3.6. Validity of the Clusters

The clustering analysis without WMH burden variables identified 4 clusters (appendix 5) and assigned 3 individuals to cluster 1' (mean age: 63.33 years, SD=12.42), 30 to cluster 2' (mean age 59.900 years, SD=6.929), and 44 to cluster 3' (mean age 57.750 years, SD= 7.716) and 13 do cluster 4' (mean age 65.92 years, SD=5.251).

Cluster 1 is negligible due to its low number of patients. The cluster 3' profile is defined by low WMH burden, better cognitive performance, and a high psychiatric symptoms score. The cluster 4' profile is characterized by a high WMH lesion burden, worse cognitive performance, late onset of psychiatric illness, and fewer psychiatric symptoms (supplementary material).

A Silhouette Cluster Analysis was conducted to assess the quality of clustering in the two analyses. The results revealed that the first clustering analysis, which included the WMH variables, presented a mean total silhouette score of 0.152 (min = -0.032, max = 0.321), while the second clustering analysis, which excluded the WMH variables from the analysis, presented a mean total silhouette score of 0.125 (min =-0.084, max =0.493). This reflects that the introduction of WMH variables had a structuring effect on the clusters.

4. Discussion

To our knowledge, this is the first study that performs a cluster analysis including sociodemographic variables, psychiatric symptoms, cognitive symptoms, and WMH. The data-driven approach allowed a better analysis of clinical heterogeneity, overcoming limitations and biases imposed by strict diagnostic assumptions. Thus, this method made it possible to identify patterns not detected by traditional clinical recognition of diagnosis.(Marquand et al., 2016) Multimodal assessment and multiplicity correction provided robustness to this study.

4.1. White Matter Hyperintensities

WMH of presumed vascular origin are frequent findings in psychiatric patients, being defined as subcortical signal abnormalities, hyperintense on T2-weighted MRI sequences. These lesions are markers of cerebral small vessels disease (CSVD) which is associated with cognitive decline, dementia, motor impairment, stroke, and excess risk of long-term mortality. (S. Debette & Markus, 2010; Duering et al., 2023; Hamilton et al., 2021; Hu et al., 2021a; Yi et al., 2024)

The main risk factor for WMH is age (Hamilton et al., 2021; Hu et al., 2021b), followed by vascular risk factors, especially hypertension and diabetes mellitus.(Chojdak-Łukasiewicz et al., 2021) The overall prevalence of WMH ranges from 11 to 21% in adults aged 55 to 75 years, up to 100% after the age of 90 years.(Garde et al., 2000; Wardlaw, 2001; Ylikoski et al., 1995)

The clinical relevance of WMH in psychiatric population is not yet been completely understood, but appear to impact the clinical presentation, evolution, and treatment outcome of psychiatric diseases. Meta-analysis studies have reported a higher prevalence of WMH in patients with depression and BD.(Silva et al., 2024; Wang et al., 2014) The lesion burden is associated with a more severe and chronic course of depression, including worse response to treatment.(O'Brien et al., 1998; Simpson et al., 1997)

4.2. Clusters as Neuropsychiatric Phenotypes

The 3-cluster solution revealed clinical phenotypes that can be distinguished based on cognitive, psychiatric and neurobiological factors. In particular, the variable WMH burden has been shown to confer consistency to the clusters, confirming its role in the phenotypic classification of patients with major psychiatric disorders.

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Clusters 1 and 3 simultaneously aggregate the patients with a late onset psychiatric illness and the patients with high prevalence of vascular risk factors. This finding reinforces the need for aggressive screening and control of vascular risk factors in psychiatric patients, without neglecting populations with a late onset disease who, although with less exposure to antipsychotics, appear prone to these factors.

Cluster 1 corresponds to the "vascular-cognitive" phenotype. These patients exhibit a high burden of WMH and significantly lower scores in the domains of orientation, attention, visuospatial/executive, naming, and language.

The cluster 2 is the "low vascular-psychiatric" phenotype, defined as low vascular risk, high incidence of psychiatric symptoms of multiple domains, better cognition, and low burden of WMH. This is a phenotype with low vulnerability to cerebral small vessels disease.

Cluster 3 presents a "vascular-depressive/apathy" phenotype, with the highest burden of WMH, particularly deep parietal lesions, high incidence of depressive and apathy symptoms and better cognitive performance.

4.3. Mechanistic Approach

4.3.1. Topography of WMH

The pathophysiology of WMH involves structural changes in blood vessels and impairment of autoregulatory mechanisms, leading to chronic ischemia, blood-brain barrier damage, oligodendrocytes apoptosis, hemorrhage, and inflammation.(Pantoni, 2010)

The clinical manifestations of WMH result from lesion of myelinated fibers, particularly of long-association fibers, leading to subcortical dysfunction. These clinical pictures are not intuitive, being globally characterized by cognitive dysfunction, gait impairment, and psychiatric symptoms. The topography of the lesions may influence the heterogeneity of clinical manifestation. (Huang et al., 2025; Wilmskoetter et al., 2019)

Periventricular damage appears to have more influence on cognitive decline because this area has a high concentration of long connective fibers, which connect the cortex to subcortical nuclei and other distant brain territories.(Hu et al., 2021b)

Episodic memory impairment appears to be associated with lesions in temporo-occipital cortex bilaterally, right parietal lobe, periventricular white matter, and left anterior limb of the internal capsule.(Huang et al., 2025)

Executive dysfunction has been associated with lesions in bilateral inferior frontal regions, frontal lobe, bilateral temporal-occipital cortex, right parietal periventricular region, and anterior limb of the bilateral internal capsule.(Huang et al., 2025)

The cognitive and motor impairment observed in cluster 1 is consistent with the frontal-subcortical dysfunction reported in the scientific literature.(Stéphanie Debette & Markus, 2010; Hu et al., 2021b; Pantoni, 2010)

Depressive symptoms have been associated with subcortical lesions, being hypothesized that the mood symptoms are caused by the disruption of corticostrial connections, which are known to contribute to humor and mood regulation.(de Groot et al., 2000)

Cluster 3 has the highest scores of depression and apathy domains. Depression and apathy are frequently reported in the NPI profiles of vascular cognitive impairment, reflecting the close relationship between depression and cerebral vascular diseases, especially in late-life depression.(Alexopoulos, 1997; Cummings, 2020; van Agtmaal et al., 2017)

Apathy is reported in 52% of patients with CSVD (Clancy et al., 2021; Wouts et al., 2023), being consistent with the high apathy NPI sub-score found in both cluster 1 and 3. The high prevalence of apathy in these patients may be a consequence of diaschisis, resulting from damage to longitudinal connective fibers and transneuronal degeneration.(Fahed & Steffens, 2021)

Cluster 3 also presents a higher risk of suicide, with significatively higher SBQ-R scores. The presence of WMH has been associated with an increased risk of suicide, with a 4.7-fold increase in

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rate of reported suicide attempts in patients with MDD and BD who present with WMH.(Pompili et al., 2007) Damage of association-commissural and projection fibers can result in frontal-subcortical disconnection, that manifest with impaired executive function, apathy, disinhibition, and emotional dysregulation, contributing to suicide thoughts/behaviors.(Lim et al., 2025)

4.3.2. Brain Resilience

The variability in the manifestation of WMH symptoms appears to be influenced by topography and burden, and well as genetic variability, sex, secondary neurodegeneration, comorbidities, and brain resilience. (Joshi & Galvin, 2022; Livingston et al., 2020a) Cognitive reserve and biological factors contribute to resilience, as they are related to the ability to maximize performance by recruiting alternative brain networks. Vascular risk factors, obesity, physical inactivity, lower education, low social contact, and lower intelligence are known factors to negatively influence brain resilience. (Joshi & Galvin, 2022; Livingston et al., 2020a)

Cluster 3 has a predominance of male patients. A higher prevalence of cardiovascular risk factors is observed in men (Bonberg et al., 2022a), but there is evidence of an age-related acceleration of cerebrovascular burden in woman and a higher susceptibility to the cerebrovascular consequences of type 2 diabetes, HT and smoking.(Schweitzer et al., 2024)

Women appear to be protected from WMH in middle age but became more vulnerable to it at older ages. Regarding cognitive impact of WMH burden, woman appear to have a greater cognitive reserve, but faster cognitive decline than men. (Schweitzer et al., 2024) There is a limited understating of the underlying causes of sex-related differences, but variations in endogenous sex hormones throughout a women's lifetime may play a role in the trajectory of WMH. Postmenopausal women appear to have more WMH compared to premenopausal woman and men of the same age range, reflecting a protective effect of endogenous estrogens.(Bonberg et al., 2022b; Schweitzer et al., 2024)

4.3.3. Sleep Apnea and WMH

Obstructive sleep apnea (SA) is associated with hypoperfusion/hypoxia caused by recurrent collapse of the upper airway during sleep, leading to brain arousal and oxygen desaturation. Although SA increases cardiovascular and metabolic risk, a significant dose-dependent association has been reported between SA and WMH, even after adjusting for cardiovascular risk factors.(Ho et al., 2018; Huang et al., 2020; Zacharias et al., 2021)

Emergent research on the brain glymphatic system has supported the hypothesis that this system plays a fundamental role in the regulation of cerebral interstitial fluid, the clearance of metabolic waist, and brain immunity. The kinetics of the brain glymphatic system appears to be regulated by sleep, and an impairment of brain glymphatic system of patients with SA has been reported. Thus, SA can affect glymphatic clearance, contributing to lower resilience to brain insults such as hypoperfusion/hypoxia and inflammation. (Hablitz & Nedergaard, 2021; Roy et al., 2022) The association between SA and WMH reinforces the need for diagnosis and treatment of SA as a strategy to prevent WMH progression.

4.4. Therapeutic Implications

4.4.1. Phenotype-Guided Strategies

The results of our research demonstrate the need for personalized, phenotype-driven strategies Figure 3. We propose a systematic identification of patients with vascular risk factors and WMH in patients with major psychiatric disorders. To this end, all patients should undergo hypertension and metabolic assessment, sleep apnea screening (STOP-BANG), and neuroimaging evaluation. Subsequently, they should be screened for cognitive impairment with the MoCA, in addition to the psychopathological evaluation.

We propose that patients with major psychiatric disorders and vascular risk factors, regardless of whether they present with WMH, undergo aggressive control/treatment of hypertension, diabetes,

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dyslipidemia, and SA. Angiotensin-converting enzyme inhibitors are the antihypertensive medications most consistently associated with decreased WMH progression. (Goldstein et al., 2022; Su et al., 2021)

Patients with a vascular-cognitive phenotype, in addition to psychiatric treatment, should undergo cognitive and physical rehabilitation focusing on executive functions and psychomotor speed training. Psychotropic medication should be reviewed, avoiding medications with intense sedative and anticholinergic effects, reducing the negative impact on cognitive function. (Peralta et al., 2024)

The antidepressant treatment strategy for patients with the vascular-depressive/apathy phenotype should address the worse outcome of antidepressant treatment, possibly because of executive dysfunction (Egglefield et al., 2025a), as well as the apathy component, having in mind that SSRIs are associated with increased rates of apathy (Lanctôt et al., 2023). Psychopharmalogical treatments with some evidence of efficacy in treating apathy are methylphenidate and ketamine. (Costello et al., 2024; Egglefield et al., 2025b) Other potentiation strategies with positive evidence are repetitive transcranial magnetic stimulation, behavioral therapy and cognitive rehabilitation. (Costello et al., 2024; Egglefield et al., 2025b)

Finally, we suggest strategies for screening and preventing suicide risk. There is no specific method recommended for population with cerebral small vessels disease.

Psychopharmacologic drugs with proven efficacy in suicide prevention include lithium, anticonvulsant mood stabilizers, dopamine antagonists, particularly clozapine, and antidepressants. Non-pharmacological methods with proven efficacy in suicide prevention include electroconvulsive therapy, psychotherapy, and restriction of access to lethal means.(Zalsman et al., 2016)

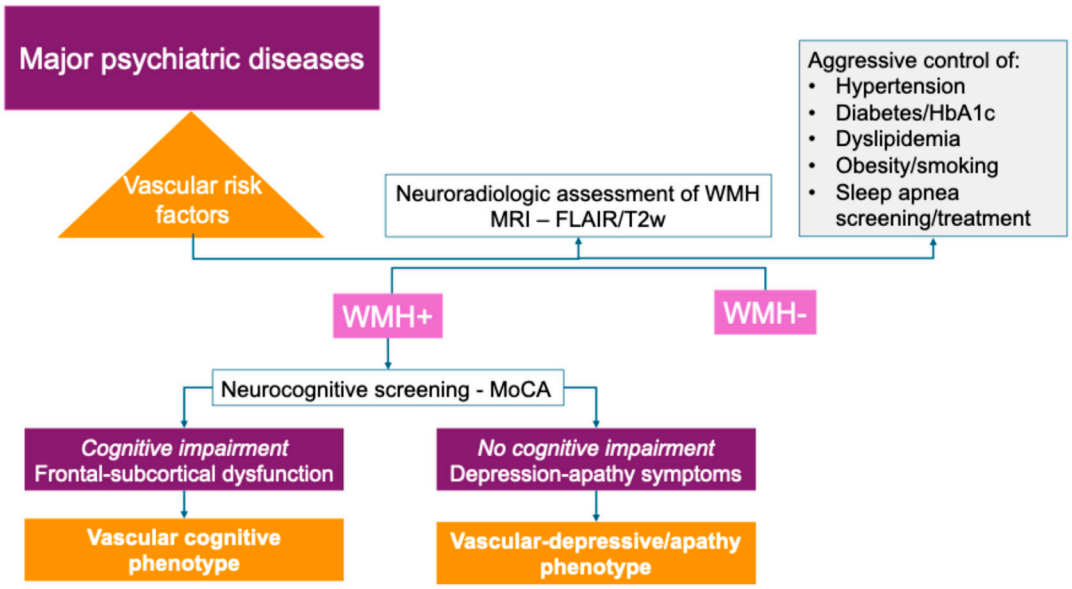

Figure 3. Clinical algorithm for identification of vascular neuropsychiatric phenotypes.

4.4.2. Promotion of Resilience – "Vascular Safety" and Plasticity

For vascular phenotypes the use of anticholinergic medications should be avoided because, in addition to the cognitive effects referred before, these drugs cause hypotension, worsening of cerebral perfusion, and sedation. Whenever possible, metabolic-friendly psychotherapeutic regimes should be the first choice.(Hilmer & Gnjidic, 2022)

Dementia risk factors control strategy is particularly important for vascular phenotypes, as these patients are at a higher risk of cognitive impairment and dementia due to the WMH. Of the 12 modifiable risk factors identified in the 2020 Lancet Commission report, the most important measures

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for risk reduction for the patients with vascular phenotypes, are: regular physical activity, healthy diet (Mediterranean type), weigh control, smoking abstinence, social and cognitive engagement. (Livingston et al., 2020b)

4.5. Methodologic Aspects and Limitations

This study has several limitations that should be considered to shape future directions.

The sample size provided an adequate statistical power to identify three cluster of patients, but a larger sample would be more representative of acute psychiatric inpatients and would possibly allow the identification of more homogeneous clusters. The sample is restricted to a subgroup of psychiatric population, not allowing the generalization of the results.

Another potential limitation is self-reporting data, such as physical activity and family history of psychiatric illnesses.

The multidimensionality is an advantage in exploratory studies but may decrease the consistency of the clusters. The low silhouette index in both cluster analyses may be the result of the high dimensionality of the data.

Quantification and localization of WMH is a challenging procedure due to the variability of topography and format of the lesions. There are different methods for WMH assessment: semi-quantitative methods, which include the visual rating scales such as Fazekas scale and Modified Scheltens Rating Scale, and quantitative volumetric analyses. The use of visual rating scales is more practical for clinical use but has some limitations. First, the use of categorical classifications restricts the range of values, limiting the power of association.(Iorio et al., 2013a) Secondly, the progression of grades in Fazekas scale is not proportional, meaning that progression from grade 1 to 2, and from grade 2 to 3 does not imply the existence of twice as many lesions. This results in an artificial gradation of a lesional continuum.

Finally, these methods present reproducibility problems due to interobserver disagreement. (Iorio et al., 2013b; Kapeller et al., 2003)

On the other hand, quantitative volumetric methods range from manual lesion outlining, to fully automated detection of WMH. These methods have the advantage of being more precise but require a highly trained operator due to their complexity of use.(Iorio et al., 2013b)

In this research, WMH burden can differentiate clusters when assessed by the MSRS, particularly, cluster 3 has the highest MSRS deep parietal lesions scores. This suggests that regional/quantitative measures (MSRS) are more sensible than global graduation measures (Fazekas) for assessing phenotypes based on WMH topography. The Fazekas scale may be insufficient to differentiate subtle profiles of patients with CSVD. The use of MSRS for WMH assessment may improve prognosis and therapeutic decision-making.

Regarding the cognitive assessment instruments, the MMSE had a poor correlation with WMH burden. This can be explained by its lower sensitivity to mild cognitive impairment and cognitive dysfunction not related to Alzheimer's disease.

In the MMSE the short-memory and the visuospatial processing tasks have low complexity, so making this assessment test less able to detect subtle cognitive deficits and deficits involving executive function.(de Boer et al., 2025)

Since WMH are associated with subcortical damage, leading to executive dysfunction (doi:10.1038/nrneurol.2015.10), the MMSE is an inappropriate instrument for assessment in populations with cognitive impairment associated with microvascular damage. The MoCA has greater sensitivity and better discriminatory power, making it a more appropriate tool for cognitive screening of preclinical or mild cognitive impairment patients.(de Boer et al., 2025)

5. Conclusions

In conclusion, this study provides information on the existence of different subgroups of psychiatric patients identified by psychiatric symptoms, cognitive symptoms, and WMH burden.

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This reflects how multiple factors interact with disruption of neurocircuits, manifesting in varying clinical presentations.

These data are important for identifying patients who could benefit from therapeutic adjustments or different preventive strategies for a better outcome.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Dr. Tânia Silva: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing– original draft, Writing– review & editing. Dr. César Nunes: Methodology, Software, Validation, Visualization, Writing– review & editing. Dr. Andreia Ribeiro: Data curation, Investigation. Prof. Dr. Isabel Santana: Conceptualization, Investigation, Project administration, Supervision, Validation. Prof. Dr. Joaquim Cerejeira: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing– review & editing.

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Disclosure statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A

Appendix A.1. Exclusion Criteria

Patients were excluded if they:

- had a known diagnosis of monogenic forms of cerebral small vessel disease (CADASIL, CARASIL, familial cerebral amyloid angiopathy, HANAC, Fabry disease, homocystinuria, MELAS, HDLS, RVCL, Axenfeld-Rieger syndrome);
- met DSM-5 criteria for comorbid diagnosis of intellectual disabilities, autism spectrum disorders, feeding and eating disorders and alcohol/substance use disorders;
- presented a state of delirium according to clinical criteria;
- had been diagnosed with major neurological diseases (e.g., Parkinson Disease, Huntington disease, amyotrophic lateral sclerosis, epilepsy);
- met criteria for Dementia according to international standardized criteria (Alzheimer dementia, Frontotemporal dementia, multi-infarct vascular or Lewy body dementia);
- presented radiological evidence of non-vascular demyelinating syndromes, unilateral cerebral microvascular lesions or known history or neuroradiological signs of great vessel stroke;
- had clinically significant structural brain damage or CNS trauma in the past;
- had history of HIV or spirochetal infection of CNS (e.g., syphilis, borreliosis, or Lyme disease), acute medical illness, autoimmune disorders, history of cancer within the past 5 years, recent major surgery, untreated hypothyroidism or vitamin deficiency (cobalamin, folate and vitamin D);
- were under legal custody (imprisonment).

Appendix A.2. Neuroimaging Protocol

- Neuroimaging protocol: 3-T Siemens Magneton Vida scanner. Magnetization-prepared rapid gradient- echo T1- weighted images (MP-RAGE) acquired in sagittal plane and T2/FLAIR

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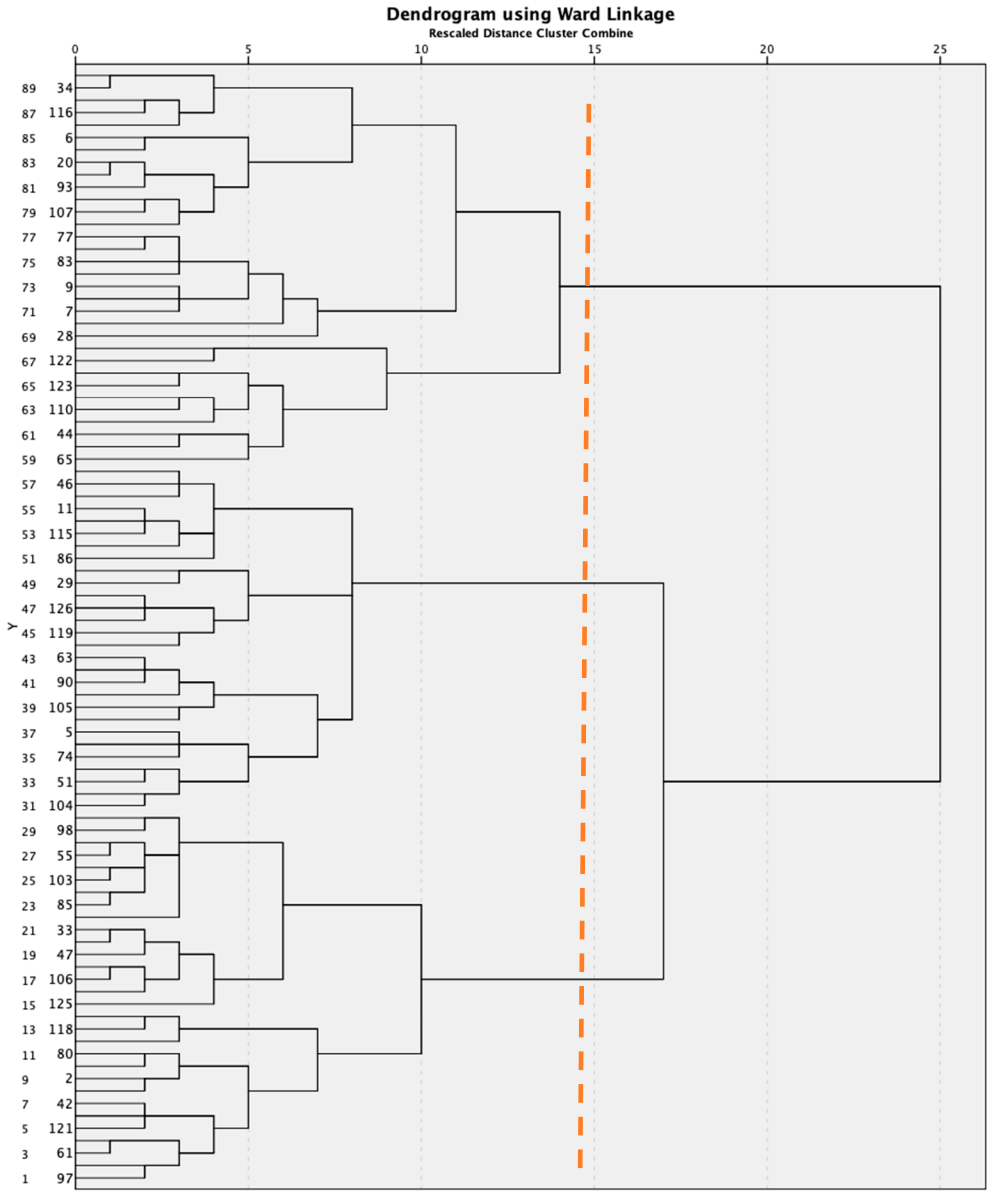
images acquired in the axial plane. FLAIR: repetition time 9000 ms, echo time 91 ms, inversion time 2500 ms, flip angle 150°, slice thickness 3 mm, field of view 256 × 256 mm. T2-weighted: repetition time 5500 ms, echo time 108 ms, 130° flip angle, slice thickness 3 mm, field of view 256 × 256 mm. T1-3D MP-RAGE (when available): repetition time 2000 ms; echo time 2.2 ms; inversion time 900 ms; flip angle 8°; parallel imaging - GRAPPA 2), voxel size 0.5 mm × 0.5 mm x 0.5; matrix size 256 × 256; number of slices 352.

Appendix A.3. Dendrogram of Ward's Method Including All Variables in the Analysis. The Dendrogram Shows the Distance Between Clusters. The Orange Dotted Line Indicates the Cluster Selection Point



Appendix A.4. Tables of Findings

Table A1. Demographic characteristics for three-cluster solution with k-means clustering method. M – mean, SD - standard deviation, F – F ratio between group effect (ANOVA), χ2 - Chi-square statistic.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Stat.	Sig.
Age, M (SD)	66.15 (7.20)	57.68 (7.20)	62.05 (5.02)	F=8.60	**0.001**
Biologic sex (Male), %	15.4%	22.4%	57.9%	χ2=10.11	**0.006**

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Educational level, %	4y: 69.2 9y: 23.1 12y: 0 >12y: 7.7	4y: 22.4 9y: 8.6 12y: 17.2 >12y: 51.7	4y: 52.6 9y: 21.1 12y: 10.5 >12y: 15.8	$\chi 2$=22.30	**0.001**

Table A2. Psychiatric history and family history of psychiatric disease for three-cluster solution with k-means clustering method. FH - family history, M – mean, SD - standard deviation, Stat. – statistics, Sig. – significance level, F – F ratio between group effect (ANOVA), $\chi 2$ - Chi-square statistic, N/S – p-value not significant. (1) KW – Kruskal Wallis test, (2) Chi-square test.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Stat.	Sig.
Age of psychiatric illness onset, M (SD)	44.69 (20.14)	37.36 (13.31)	45.63 (13.08)	F=3.10	**0.05**
Number of psychiatric hospitalizations, M (SD)	2.38 (1.75)	3.13 (3.62)	2.15 (1.53)	(1)	N/S
FH of dementia before 65y, %	30.8	5.2	0	$\chi 2$=11.73	**0.003**
FH of dementia after 65y, %	23.1	19	42.1	(2)	N/S
FH of MDD or BD, %	15.4	39.7	52.6	(2)	N/S
FH of psychosis spectrum disorders, %	7.7	17.2	5.3	(2)	N/S
FH of suicide, %	0	13.8	15.8	(2)	N/S

Table A3. Medical history for three-cluster solution with k-means clustering method. M – mean, SD - standard deviation, Stat. – statistics, Sig. – significance level, SA – sleep apnea, Inc. – Increased risk of sleep apnea, Low – Low risk of sleep apnea, ASA – acetyl salicylic acid, χ^2 - Chi-square statistic, Sed. – Sedentary, I. Act - Irregularly active, Act – Active, V. act – Very active, N/S – p-value not significant. (1) Chi-square test, (2) ANOVA.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Stat.	Sig.
Tobacco use, %	7.7	24.1	21.1	(1)	N/S
Hypertension, %	76.9	43.1	84.2	$\chi 2$=12.38	**0.002**
Mellitus diabetes, %	53.8	1.7	57.9	$\chi 2$=36.89	**<0.001**
Dyslipidemia, %	92.3	75.9	94.7	(1)	N/S
Body mass index, M (SD)	28.48 (4.13)	26.26 (4.67)	28.28 (3.51)	(2)	N/S
Risk or sleep apnea, %	SA: 15.4 Inc.: 38.5 Low: 46.2	SA: 6.9 Inc.: 24.1 Low: 69	SA: 21.1 Inc.: 52.6 Low: 26.3	$\chi 2$=11.51	**0.021**
Physical activity, %	Sed.: 53.8 I. Act: 23.1 Act: 23.1 V. Act: 0	Sed.: 53.4 I. Act: 25.9 Act: 20.6 V. Act: 0	Sed.: 42.1 I. Act: 21.1 Act: 21.1 V. Act: 15.8	$\chi 2$=15.79	**0.045**
Treatment with anticoagulants, %	0	6.9	5.3	(1)	N/S
Treatment with ASA, %	23.1	0	15.8	$\chi 2$=12.31	**0.002**
Treatment with clopidogrel, %	0	0	0		
Treatment with anti-dyslipidemia drugs, %	69.2	22.4	84.2	$\chi 2$=26.94	**<0.001**
Treatment with statins, %	69.2	22.4	78.9	$\chi 2$=23.85	**<0.001**
Treatment with anti-hypertensive drugs, %	46.2	27.6	78.9	$\chi 2$=15.75	**<0.001**
Treatment with antidiabetic drugs, %	30.8	0	52.6	$\chi 2$=32.85	**<0.001**
Treatment with metformin, %	30.8	0	52.6	$\chi 2$=32.85	**<0.001**
Treatment with insulin, %	23.1	0	5.3	$\chi 2$=13.35	**0.001**
Treatment with typical antipsychotics, %	7.7	13.8	0	(1)	N/S

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Treatment with atypical antipsychotics, %	100	89.7	84.2	(1)	N/S
Treatment with lithium, %	0	13.8	15.8		N/S
Treatment with valproate/valproic acid, %	15.4	34.5	5.3	$\chi2$=7.24	**0.027**
Treatment with benzodiazepines, %	76.9	93.1	89.5	(1)	N/S
Treatment with tricyclic antidepressants, %	0	6.9	5.3	(1)	N/S
Treatment with SSRI, %	38.5	36.2	68.4	$\chi2$=6.19	**0.045**
Treatment with other AD, %	15.4	22.4	31.6	(1)	N/S
Treatment with psychostimulants, %	0	1.7	4.4	$\chi2$=7.37	**0.025**

Table A4. Cognitive performance scores for three-cluster solution with k-means clustering method. M – mean, SD - standard deviation, Stat. – statistics, Sig. – significance level, MoCA - Montreal Cognitive Assessment, MMSE - Mini-Mental State Examination, F – F ratio between group effect, KW – Kruskal-Wallis H, N/S – p-value not significant. (1) Kruskal-Wallis test, (2) ANOVA.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Stat.	Sig.
MoCA total (adapted), M (SD)	13.07 (3.94)	22.51 (3.47)	22.57 (2.91)	KW=28.25	**<0.001**
MoCA visuospatial/ executive subtest, M (SD)	1.46 (1.19)	3.29 (1.42)	2.89 (1.24)	KW=15.35	**<0.001**
MoCA naming subtest, M (SD)	2 (1.35)	2.91 (0.33)	3 (0)	KW=15.64	**<0.001**
MoCA attention subtest, M (SD)	2.00 (1.63)	4.62 (1.44)	4.78 (1.35)	F=18.65	**<0.001**
MoCA language subtest, M (SD)	1.53 (0.96)	2.27 (0.69)	2.05 (0.97)	KW=6.63	**0.034**
MoCA abstraction subtest, M (SD)	0.53 (0.77)	1.44 (0.72)	1.26 (0.80)	F=7.67	**<0.001**
MoCA memory/delayed recall subtest, M (SD)	0.76 (1.23)	1.67 (1.39)	1.78 (1.87)	(1)	N/S
MoCA orientation subtest, M (SD)	4.84 (1.34)	5.82 (0.46)	5.94 (0.22)	KW=16.20	**<0.001**
MMSE total, M (SD)	22.92 (3.12)	27.60 (2.00)	27.68 (1.73)	KW=22.02	**<0.001**
MMSE orientation subtest, M (SD)	8.07 (1.18)	9.63 (0.74)	9.31 (1.66)	KW=22.28	**0.001**
MMSE registration subtest, M (SD)	3.00 (0)	3.00 (0)	3.00 (0)		
MMSE attention and calculation subtest, M (SD)	2.53 (1.71)	4.27 (1.03)	4.63 (0.68)	KW=15.98	**<0.001**
MMSE recall subtest, M (SD)	2.00 (0.91)	2.39 (0.74)	2.10 (0.56)	(1)	N/S
MMSE language subtest, M (SD)	6.92 (1.18)	7.56 (0.62)	7.63 (0.68)	(1)	N/S
MMSE copying subtest, M (SD)	0.46 (0.51)	0.75 (0.43)	0.78 (0.41)	(2)	N/S
Psychomotor velocity, M (SD)	40.61 (8.69)	50.43 (9.93)	50.21 (10.30)	KW=11.88	**0.003**

Table A5. Psychopathologic symptoms for three-cluster solution with k-means clustering method. M – mean, SD - standard deviation, Stat. – statistics, Sig. – significance level, NPI - Neuropsychiatric inventory, SBQ-R - Suicide Behaviors Questionnaire, GAF - Global Assessment of functioning scale, F – F ratio between group effect, KW – Kruskal-Wallis H, $\chi2$ - Chi-square statistic, N/S – p-value not significant. (1) ANOVA, (2) Kruskal-Wallis test, (3) Chi-square test.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Stat.	Sig.
NPI delusions, M (SD)	5.61 (5.82)	6.10 (5.32)	4.10 (5.31)	(1)	N/S
NPI hallucinations, M (SD)	0.84 (1.72)	2.20 (3.94)	1.15 (3.07)	(2)	N/S
NPI agitation, M (SD)	6.00 (5.09)	4.10 (4.67)	2.47 (3.40)	(1)	N/S
NPI depression, M (SD)	2.53 (4.52)	3.91 (4.89)	7.52 (5.23)	F=5.04	0.008
NPI anxiety, M (SD)	3.00 (3.89)	5.10 (3.89)	6.63 (4.69)	(1)	N/S
NPI euphoria, M (SD)	4.30 (5.21)	2.96 (4.55)	2.42 (4.64)	(1)	N/S
NPI apathy, M (SD)	2.69 (4.71)	1.29 (2.97)	4.78 (5.42)	KW=10.48	0.005
NPI disinhibition, M (SD)	3.53 (3.92)	1.84 (2.83)	1.36 (3.20)	(2)	N/S

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NPI irritability, M (SD)	4.00 (4.63)	3.08 (4.63)	2.89 (4.53)	(1)	N/S
NPI motor behavior, M (SD)	2.30 (3.98)	2.17 (3.98)	1.78 (3.04)	(2)	N/S
NPI nocturnal behavior, M (SD)	7.00 (4.45)	6.89 (4.94)	7.15 (4.86)	(1)	N/S
NPI appetite, M (SD)	1.38 (3.59)	2.18 (3.65)	3.73 (4.34)	(2)	N/S
NPI total	43.23 (26.12)	41.87 (16.59)	46.05 (18.90)	(2)	N/S
SBQ-R, M (SD)	5.38 (3.47)	5.79 (3.81)	9.73 (4.91)	F=7.52	<0.001
GAF, %	91 – 100%: 0 81 – 90%: 0 71 – 80%: 7.7 61 – 70%: 7.7 51 – 60%: 23.1 41 – 50%: 23.1 31 – 40%: 15.4 21 – 30%: 7.7 11 – 20%: 15.4	91 – 100%: 1.7 81 – 90%: 0 71 – 80%: 25 61 – 70%: 12.5 51 – 60%: 33.3 41 – 50%: 7.9 31 – 40%: 13.3 21 – 30%: 12.5 11 – 20%: 28.6	91 – 100%: 0 81 – 90%: 0 71 – 80%: 0 61 – 70%: 10.5 51 – 60%: 5.3 41 – 50%: 47.4 31 – 40%: 10.5 21 – 30%: 10.5 11 – 20%: 15.8	(3)	N/S

Table A6. White matter hyperintensities ratting for three-cluster solution with k-means clustering method. M – mean, SD - standard deviation, Stat. – statistics, Sig. – significance level, MSRSpv/d – Modified Scheltens Rating scale periventricular and deep white matter hyperintensities score, MSRSpv - Modified Scheltens Rating scale periventricular white matter hyperintensities score, Modified Scheltens Rating scale deep white matter hyperintensities score. F – F ratio between group effect, KW – Kruskal-Wallis H, $\chi 2$ - Chi-square statistic, N/S – p-value not significant. (1) Chi-square test, (2) ANOVA, (3) Kruskal-Wallis test.

Variables	Cluster 1, n=13	Cluster 2, n=58	Cluster 3, n=19	Test Stat.	Sig.
FAZEKAS score, %	Grade 0 – 30.8 Grade 1 – 53.8 Grade 2 – 7.7 Grade 3 – 7.7	Grade 0 – 53.4 Grade 1 - 36.2 Grade 2 – 8.6 Grade 3 – 1.7	Grade 0 – 21.1 Grade 1 - 57.9 Grade 2 – 21.1 Grade 3 - 0	(1)	N/S
MSRSpv occipital score, M (SD)	0.38 (0.76)	0.36 (0.55)	0.68 (0.67)	(2)	N/S
MSRSpv frontal score, M (SD)	1.07 (0.49)	1.12 (0.53)	1.15 (0.60)	(3)	N/S
MSRSpv lateral walls score, M (SD)	0.92 (0.49)	0.87 (0.56)	1.00 (0.57)	(3)	N/S
MSRSpv total score, M (SD)	2.38 (1.55)	2.37 (1.39)	2.89 (1.52)	(3)	N/S
MSRSd frontal deep score, M (SD)	1.84 (1.95)	1.36 (1.65)	2.36 (2.06)	(2)	N/S
MSRS parietal deep score, M (SD)	1.38 (1.75)	1.10 (1.67)	2.47 (2.29)	F=4.02	0.021
MSRS occipital deep score, M (SD)	0.07 (0.27)	0.05 (0.39)	0.05 (0.22)	(3)	N/S
MSRS temporal deep score, M (SD)	0.23 (0.59)	0.86 (0.28)	0.15 (0.37)	(3)	N/S
MSRS deep total score, M (SD)	3.53 (3.92)	2.60 (3.37)	5.05 (4.18)	KW=6.49	0.039
MSRS total score, M (SD)	5.92 (5.26)	4.98 (4.47)	7.94 (5.46)	KW=6.06	0.048

Table A7. Multiple comparison of age between clusters with Fisher's Least Significant Difference method. CI – confidence interval, MD - Mean Difference, SE – Standard error, LB - Lower Bound, UB – Upper Bound.

Cluster	Cluster	MD	SE	Sig.	95% CI	
					LB	UP
1	2	8.46419*	2.18799	<.001	4.1153	12.8131
	3	4.10121	2.56642	.114	-.9998	9.2023

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2	1	-8.46419*	2.18799	<.001	-12.8131	-4.1153
	3	-4.36298*	1.88476	.023	-8.1091	-.6168
3	1	-4.10121	2.56642	.114	-9.2023	.9998
	2	4.36298*	1.88476	.023	.6168	8.1091

*. The mean difference is significant at the 0.05 level.

Table A8. Results of multiple comparison analysis controlling for the False Discovery Rate (FDR) by domain (Demographics, Psychiatric History, Medical History, Cognition, Psychopathology, and WMH Burden). The Benjamini–Hochberg procedure (q=0.05) was applied. For each variable tested between clusters, the original p-value and the adjusted p-value (q-value) are showed. The correction was performed separately within each homogeneous domain to control for the expected false positive rate in each thematic block. FDR - False Discovery Rate, q-value - p-value ajusted by FDR, WMH - white matter hyperintensities, MSRS - Modified Scheltens Rating Scale, MoCA - Montreal Cognitive Assessment, MMSE - Mini-Mental State Examination, NPI - Neuropsychiatric Inventory, SBQ-R - Suicide Behaviors Questionnaire–Revised.

Domain	Variable	Original p-value	FDR-adjusted p-value	Significant?
Demographics	Age	0.001	0.003	Yes
Demographics	Biological sex	0.006	0.009	Yes
Demographics	Education	0.001	0.003	Yes
Psychiatric History	Age of onset	0.050	0.060	No
Psychiatric History	Family history of dementia <65	0.003	0.009	Yes
Medical History	Hypertension	0.002	0.006	Yes
Medical History	Diabetes mellitus	0.001	0.003	Yes
Medical History	Sleep apnea risk	0.021	0.040	Yes
Medical History	Physical activity	0.045	0.060	No
Medical History	ASA / Statins / Antidiabetics	≤0.001	≤0.003	Yes
Medical History	Psychostimulants	0.025	0.040	Yes
Cognition	MoCA total	0.001	0.003	Yes
Cognition	MoCA subtests	≤0.034	≤0.040	Yes
Cognition	MMSE total	0.001	0.003	Yes
Cognition	Psychomotor speed	0.003	0.009	Yes
Psychopathology	Depression (NPI)	0.008	0.020	Yes
Psychopathology	Apathy (NPI)	0.005	0.015	Yes
Psychopathology	SBQ-R (suicide risk)	0.001	0.003	Yes
WMH Burden	MSRSd parietal	0.021	0.040	Yes
WMH Burden	MSRSd	0.039	0.045	Yes
WMH Burden	MSRS total	0.048	0.050	Borderline

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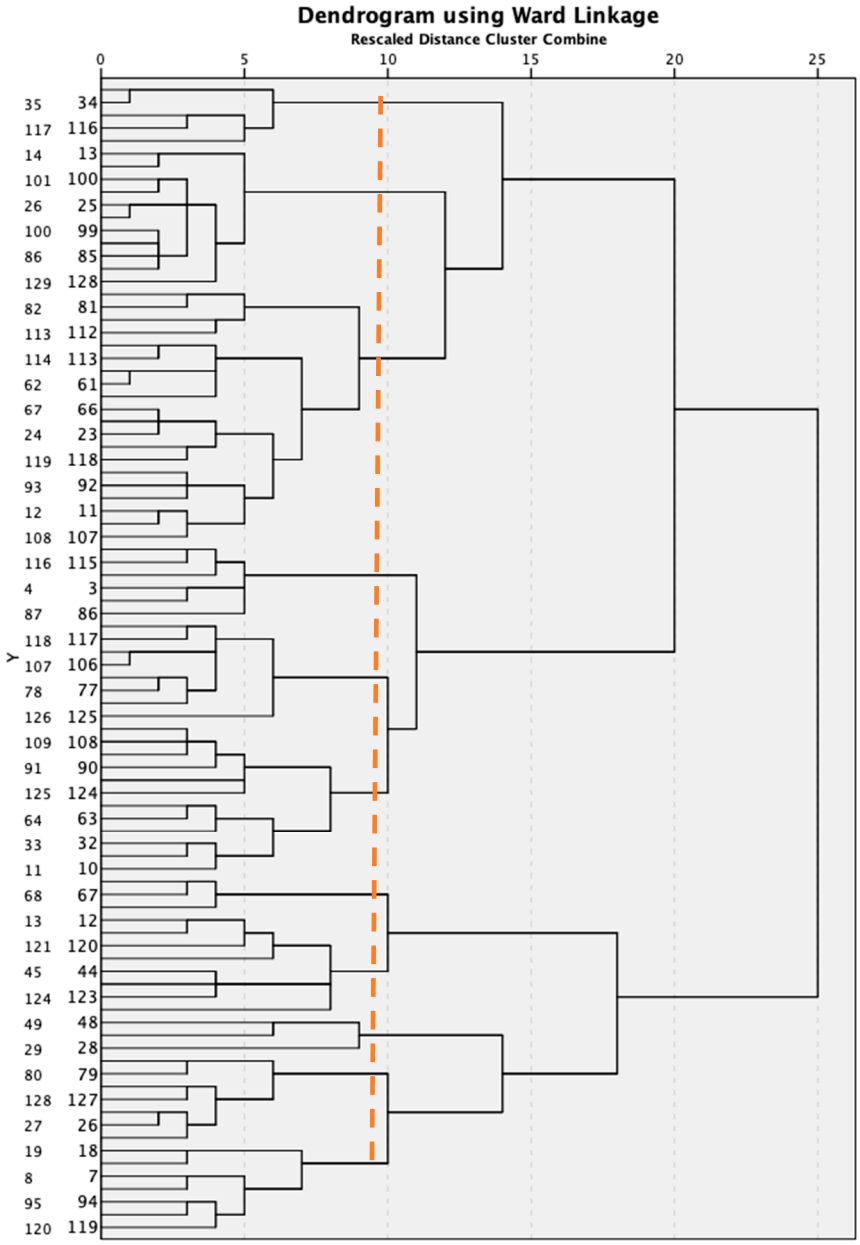
Appendix A.5. Dendrogram of Ward's Method Excluding WMH Burden Variables of the Analysis. The Dendrogram Shows the Distance Between Clusters. The Orange Dotted Line Indicates the Selection Point. With a Standardization Purpose, the Same Cutoff Point from the First Analysis Was Selected



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