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Procedia Computer Science 251 (2024) 326–333

Procedia Computer Science

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The 14th International Conference on Current and Future Trends of Information and Communication Technologies in Healthcare (ICTH 2024)
October 28-30, 2024, Leuven, Belgium

Clustering of longitudinal Clinical Dementia Rating data to identify predictors of Alzheimer's disease progression

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Abstract

Clinical Dementia Rating (CDR) is a common tool to assess cognitive and functional abilities in the context of Alzheimer's disease (AD). It is a structured interview that encompasses evaluation across six specific domains. However, AD's initial stages may not lead to a uniform cognitive decline across all cognitive domains. The main aim of this study is to evaluate the prognostic utility of individual CDR domains in predicting the progression of AD dementia over a five-year longitudinal period among an elderly cohort. Initially, a longitudinal-cluster analysis was conducted using five-point longitudinal data to categorize subjects into clusters based on the progression of CDR domains during the follow-up. Then, a statistical analysis was performed on the identified clusters to ascertain whether, at the baseline, patients exhibiting stability have different profiles about CDR domains compared to patients who converted to an AD during the whole follow-up period. Results show that the risk of AD progression was mainly related to problems with Orientation and Judgment at the baseline.

Keywords: Alzheimer's disease; Cognitive Decline; Clinical Dementia Rating; Longitudinal Clustering; Statistical Analysis

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia among the elderly, marked by pathological alterations in the brain that manifest approximately 10 to 15 years before the clinical symptoms [5]. Unfortunately, there are currently no definitive therapies available for this medical condition. Nevertheless, identifying reliable predictors for dementia in the early stages could potentially contribute to ameliorating disease progression. Hence, interventions

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1877-0509
10.1016/j.procs.2024.11.117

could be implemented for individuals with the highest vulnerability to mitigate their risk, potentially enabling them to undergo prolonged periods of cognitive acuity.

Due to its significance, identifying prognostic factors for cognitive decline in older adults has elicited considerable interest among clinical professionals and researchers. Over the past few decades, various factors, including clinical data, liquid biomarkers, and imaging biomarkers, have been the subject of comprehensive investigations [2, 17, 4, 15]. One notable variable in this regard is the acquisition of clinical data, such as neuropsychological evaluations and personal backgrounds gathered from subjects or their designated representatives. This data is a reliable and cost-efficient prognostic instrument that can be easily incorporated into clinical activities and research endeavors.

The onset of Alzheimer's Disease involves gradually worsening mild memory problems, leading to brain-function loss. According to the National Institute of Ageing and Alzheimer's Association [14], the guidelines to diagnose AD identify three stages: (1) preclinical AD, with measurable changes in biological and pathological markers but without outward changes; (2) Mild Cognitive Impairment (MCI), with observable and measurable slight memory cognitive complaints, and (3), dementia due to AD, where memory and cognitive problem prevent the patient from performing daily activities.

Studies have also indicated that not all individuals diagnosed with MCI inevitably progress to developing AD in the future [9, 11, 13]. According to clinical observations, MCI individuals can be grouped in: *MCI stables or MCIs* indicating those who persist with their initial diagnosis at subsequent assessments and *MCI progressors or MCIp* namely, those who display symptoms characteristic of AD during follow-up evaluations.

Additionally, subjects diagnosed with MCI show great variability. However, when memory impairment is the primary characteristic, it is categorized as *amnestic MCI* and is often considered a precursor to AD development. Due to its high risk for the progression [12], amnestic MCI has been becoming the focus of AD dementia prediction.

One of the first instruments introduced to study patients with different types of dementia is the Clinical Dementia Rating (CDR) Staging Instrument [10]. It characterizes cognitive and functional performance across six domains relevant to AD and related dementia, including Memory, Orientation, Judgment and Problem-Solving, Community Affairs, Home and Hobbies, and Personal Care.

The CDR assessment produces a CDR Global Score (CDR-GS) and a CDR Sum of Box (CDR-SB). CDR-GS is calculated via an algorithm with defined scoring rules [10] based on the scores of the aforementioned domains. On the contrary, the CDR-SB score is the sum of each domain score. As opposed to the CDR-GS, which is a 5-point ordinal scale ranging from 0 to 3 (no cognitive impairment = 0, very mild = 0.5, mild = 1, moderate = 2, severe = 3), the CDR-SB is a continuous measure of dementia severity ranging from 0 (no cognitive impairment) to 18 (severe cognitive impairment).

Some existing works [3, 18] have shown the predictive power of CDR-SB for AD progression in individuals with MCI. In [3], authors performed a systematic literature review to evaluate the associations between AD severity and progression as measured by CDR Global or CDR-SB scores and various factors, including comorbidity, neuropsychiatric symptoms, decline in activities of daily living, nursing home placement, and economic costs.

The results presented in [18] indicate that CDR-SB is a strong predictor of progression to dementia or regression to healthy state (normal control, NC) in pre-dementia or very mild dementia stages. Consequently, CDR may serve as a valuable tool for assessing the efficacy of pharmacological and non-pharmacological interventions in populations without dementia.

It should be noted that the early stages of AD do not necessarily result in uniform cognitive decline across all CDR domains. Rather, the deterioration of non-memory areas and their associated functions tends to occur after the memory decline. Hence, CDR sub-scale scores related to cognitive and functional domains, besides those about memory, may prove valuable in prognosticating AD progression in people with amnestic MCI. In [6], authors aimed to evaluate the predictive value of each Clinical Dementia Rating (CDR) sub-scale score for Alzheimer's disease progression in elderly subjects with amnestic mild cognitive impairment. The results suggest that the CDR Orientation subscale score, a simple and easily accessible clinical measure, may be useful in predicting AD progression in individuals with amnestic MCI in real-world clinical settings.

Our objective is to understand if each of the 6 dimensions considered by the CDR may provide insights on disease development, i.e., if they may be considered as prognostic values to identify which patients may progress towards AD. To this purpose, we rely on unsupervised techniques to unveil hidden patterns of disease progression over a 5-year follow-up period in an elderly cohort. We first performed a cluster analysis on longitudinal data to identify clusters

of subjects according to the progression of CDR domains during the follow-up. Then, we conducted a statistical analysis on the identified clusters to determine whether, at baseline, stable patients have distinct profiles in terms of CDR domains from those who experienced a conversion to AD during the follow-up. Results show that the risk of progression was mainly related to problems with Orientation and Judgment at the baseline.

2. Materials and Method

Longitudinal clustering. To assess the prognostic significance of individual CDR domains in predicting progression to AD dementia, we employed a K-means-based longitudinal clustering approach for multivariate time series to identify temporal patterns of such domains within a cohort of elderly people. This method builds on a relatively novel K-means clustering technique tailored for time series analysis, as described by [16], which aims to identify patterns in univariate time series. K-means [8] is a popular clustering algorithm that divides n elements into k clusters, assigning each observation to the cluster with the nearest centroid. This paper adopted a K-means-based longitudinal clustering method that uses soft Dynamic Time Warping (soft-DTW) distance for multivariate time series.

Datasets. The experimental analysis drew upon two datasets, OASIS3 and ADNI2, to enhance the overall generalizability of the findings. The Open Access Series of Imaging Studies-3 (OASIS3) database (http://oasis-brains.org) [7] was collected by Washington University Knight Alzheimer Disease Research Center. It includes structural and functional MRI (magnetic resonance imaging), amyloid and metabolic PET (positron emission tomography) imaging, neuropsychological testing, and clinical data. Participants were assessed through clinical protocols following the National Alzheimer's Coordinating Center Uniform Data Set (UDS). OASIS-3 documents each participant's entries in a time series. Dementia status was assessed for the UDS using the Clinical Dementia Rating (CDR) Scale, with a CDR = 0 indicating normal cognitive function, CDR = 0.5 MCI, CDR = 1 mild impairment, and CDR = 2 moderate dementia; once a participant reached CDR = 2, they no longer were eligible for in-person assessments.

On the other side, ADNI 2 [1] refers to the Alzheimer's Disease Neuroimaging Initiative 2, a follow-up study to the original ADNI. ADNI 2 extends the original ADNI project to study AD progression using neuroimaging, other blood, urine, and cerebrospinal fluid biomarkers, and clinical and neuropsychological assessments. Additionally, the participants in OASIS3 underwent cognitive decline assessment through CDR tests.

Therefore, the inclusion criteria for this study required subjects to have attended five annual visits and completed all the CDR tests at each visit. Thus, 331 participants were selected from the aforementioned datasets, with 165 individuals from the OASIS 3 and 166 from the ADNI 2.

3. Results and Discussions

As said before, a total of 331 subjects were selected at the baseline, including 131 (39.6%) individuals with CDR-GS = 0, 198 (59.8%) individuals with CDR-GS = 0.5, and 2 (0.6%) individuals with CDR-GS = 1 from ADNI 2 and OASIS 3 datasets. On average, all subjects underwent four consecutive follow-up visits after the baseline, each occurring at one-year intervals. For each visit, patients undergo MMSE test and are classified as CN, MCI, or AD. A longitudinal k-means cluster analysis was conducted to assess the progression of the six CDR domains at five different time points, including baseline and four subsequent follow-up visits, over five years. A four-cluster experimental design enabled the identification of increasingly stratified individual profiles, thereby yielding good clustering performance metrics (i.e., Silhouette score = 0.51, Calinski-Harabasz score = 698.80, and Davis-Bouldin score = 0.60). The results of the longitudinal clustering and the respective trend of each CDR domain for the follow-up period concerning each identified cluster are depicted in Figure 1. As we can see, the analysis reveals that individuals within *Cluster 1* and *Cluster 2* demonstrate a stable clinical state throughout the follow-up period, whereas individuals within *Cluster 3* and *Cluster 4* exhibit progression in cognitive and functional performance across six domains over the same period. In particular, *Cluster 1* shows a distinctive pattern of characteristics wherein individuals consistently display normal cognitive functioning and stability throughout the study period while maintaining a high level of overall health. Analogously, the pattern identified by *Cluster 2* very likely includes features that may be related to stable amnestic mild cognitive impairment. Contrarily, the pattern observed in *Cluster 3* exhibits features that could be associated with progressive amnestic mild cognitive impairment, manifesting a slight deterioration in cognitive and

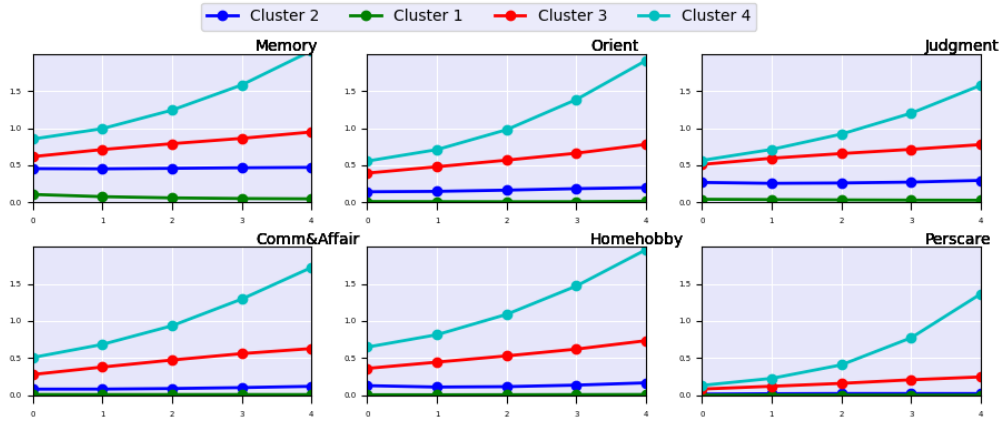


Fig. 1: Results of Longitudinal Clustering applied to CDR domains

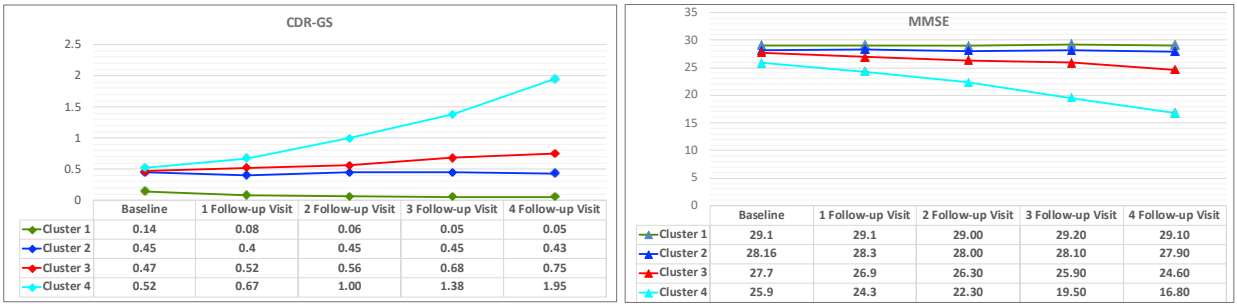


Fig. 2: Trend of CDR-GS and MMSE within each cluster

functional capacities about memory, orientation, judgment, community and affair, and home and hobbies throughout the duration of the study. Finally, the findings from *Cluster 4* illustrate a pattern that aligns with the clinical features of patients diagnosed with MCI and who exhibited notable deterioration across all six CDR domains throughout the follow-up period.

These findings are further supported by the observed trends of the CDR-GS and Mini-Mental State Examination (MMSE) within each cluster over the follow-up period computed as the average values of the MMSE and CDR-GS measurements of the subjects assigned to the respective cluster. As depicted in Fig.2, individuals of *Cluster 1* do not exhibit a decline in their overall GDS-GS and their performance on the MMSE. Individuals of *Cluster 1* show sustained stability in CDR-GS and consistently high MMSE throughout the follow-up period. On the other hand, individuals of *Cluster 3* exhibit a slight reduction in CDR-GS, alongside a decline in MMSE to an average score of approximately 24.6, a cut-off level typically associated with Alzheimer's disease patients. The onset of Alzheimer's dementia is apparent in individuals classified within *Cluster 4*.

3.1. Statistical analysis

This section analyzes the differences among clusters utilizing statistical methods to determine their degree of statistical significance. Statistical analyses were executed using Python packages, specifically *Scipy*, *Scikit-postdocs* and *Phi_K*. The Kruskal-Wallis test was employed to analyze non-normally distributed continuous data. Post hoc pairwise group comparisons were conducted using the Dunn's test. The level of significance was established at $pvalue < 0.05$. The chi-square test was employed to evaluate the differences in frequencies of categorical data, and the Phi_K test was used to evaluate the correlation between CDR domains. We use the notation $pvalue \approx 0$ when $pvalue < 1E-10$.

One of the four identified clusters, *Cluster 1*, comprises 161 individuals, with 123 from the OASIS3 dataset and 38 from the ADNI2 dataset. *Cluster 2* comprises a cohort of 96 individuals, with 20 participants derived from OASIS3

and 76 individuals from ADNI2. *Cluster 3* encompasses 53 individuals, with 17 participants from OASIS3 and 36 from ADNI2. Finally, *Cluster 4* comprises 21 individuals, with 5 participants from OASIS3 and 16 from the ADNI2.

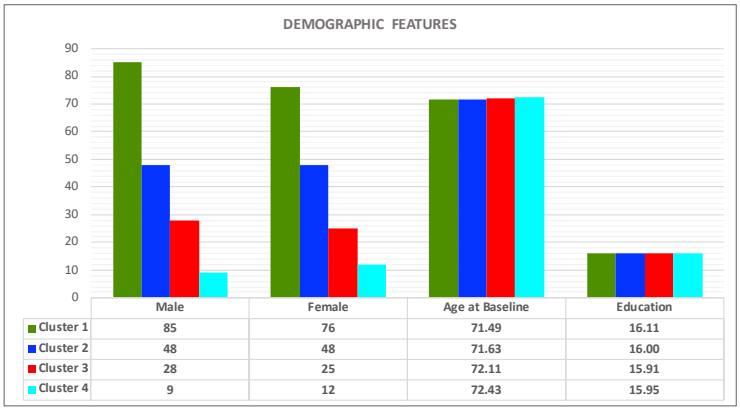
To confirm the validity of the profiles of cognitive decline identified by the longitudinal clustering, Table 1 reports the percentage distribution of cognitive normal vs impaired subjects (MCI and AD) at the baseline and the final follow-up visit within each cluster, where the diagnosis is determined by a clinician. Results of statistical tests show that the distribution of CN, MCI, and AD among clusters is statistically different ($pvalue \approx 0$). A pairwise comparison between clusters shows that statistical difference exists between each pair of clusters with respect to the distribution of CN, MCI, and AD both at baseline and at the 4^{th} follow-up visit excerpt for Cluster 3 and Cluster 4. These two clusters are not statistically different at baseline ($pvalue = 0.41$), while the difference emerges at the 4^{th} follow-up visit ($pvalue = 0.04$). Indeed, as we can see from Table 1, the greater part of individuals at baseline (73.4%) are diagnosed as cognitively normal, and part of the MCI experienced a reversion to CN at the 4^{th} follow-up visit. Among 161 individuals belonging to Cluster 1, 80,6% are CN, 17,5% MCI, and only 1.9% are AD at the 4^{th} follow-up visit. Cluster 2 and Cluster 3 have the greater part of MCI at baseline (84.4% and 73.6%), whilst the greater part of individuals (i.e., 79.2%) within Cluster 2 are confirmed with an MCI diagnosis at the 4^{th} follow-up visit, the greater part of individuals (i.e., 73.6%) in Cluster 3 is diagnosed with a progression toward AD at the 4^{th} follow-up visit. All the MCI individuals in Cluster 4 experienced a progression toward AD at the 4^{th} follow-up visit.

Hence, we consider the composition of the clusters from the point of view of demographics and cognitive functions at the baseline to detect statistical differences among clusters that can indicate a progression toward cognitive decline.

The demographic features of individuals within each cluster are summarized in Fig.3. There is no significant difference among individuals of different clusters concerning gender, age at baseline, and education level, as shown by the results obtained from the statistical tests: i.e., Age: $pvalue = 0.9$, Education: $pvalue = 0.83$, and Gender: $pvalue = 0.84$.

The percentage distribution of normal vs impaired subjects at the baseline visit for each CDR domain in the identified clusters is reported in Table 2. As we can see, all clusters are statically different in all CDR domains, with almost all showing a $pvalue \approx 0$. This difference is also maintained during the whole follow-up.

Hence, Fig.4 shows the significance plots derived from the pairwise comparison between clusters using post-hoc statistical analysis. First, for the Memory domain, *Cluster 1* is statistically different from all other clusters from the baseline visit and during the follow-up period. This finding corroborates the indication that individuals in *Cluster 1* do not manifest statistically significant memory-related concerns at baseline and similarly maintain stability during the follow-up period as opposed to individuals in other clusters. *Cluster 2* does not exhibit statistically significant differences from *Cluster 3* solely at the baseline visit; however, it does demonstrate statistically significant differences from the other clusters at the follow-up visits. This finding confirms that individuals in *Cluster 2* and individuals in *Cluster 3* show memory-related concerns at baseline. However, the difference between the two clusters became statistically significant during the follow-up period, as individuals in *Cluster 3* exhibited a memory decline, while those in *Cluster 2* maintained stability. As expected, *Cluster 2* is statically different from *Cluster 4* starting from the baseline visit. In the domain of Community & Affairs, it is observed that all clusters exhibit a statistically significant



Features	p-value
Gender	0.84
Age at Baseline	0.9
Education	0.83

Fig. 3: Demographic features of individuals within cluster

Diagnosis	**Cluster 1** (N = 161)	**Cluster 2** (N = 96)	**Cluster 3** (N = 53)	**Cluster 4** (N = 21)
CN				
Baseline	118 (73.3%)	10 (10.4%)	4 (7.5%)	0 (0.0%)
4^{th} Follow-up Visit	129 (80.1%)	8 (8.3%)	1 (1.9%)	0 (0.0%)
MCI				
Baseline	42 (26.1%)	81 (84.4%)	39 (73.6%)	16 (76.2%)
4^{th} Follow-up Visit	28 (17.4%)	76 (79.2%)	12 (22.6%)	0 (0.0%)
AD				
Baseline	1 (0.6%)	5 (5.2%)	10 (18.9%)	5 (23.8%)
4^{th} Follow-up Visit	3 (1.9%)	11 (11.6%)	39 (73.6%)	21 (100%)

Table 1: Percentage distribution of cognitive normal vs impaired subjects (MCI and AD) at the baseline and the final follow-up visit within clusters.

CDR-Domain	**Cluster 1** (N = 161)	**Cluster 2** (N = 96)	**Cluster 3** (N = 53)	**Cluster 4** (N = 21)	**p-value**
Memory					≈ 0
0	118 (73.3%)	10 (10.4%)	4 (7.5%)	0 (0.0%)	
≥ 0.5	43 (26.7%)	86 (89.6%)	49 (92.5%)	21 (100%)	
Orientation					≈ 0
0	158 (98.2%)	68 (70.8%)	21 (39.7%)	6 (28.5%)	
≥ 0.5	3 (1.8%)	28 (29.2%)	32 (60.3%)	15 (71.5%)	
Judgment					≈ 0
0	147 (91.3%)	43 (44.8%)	12 (22.6%)	1 (4.8%)	
≥ 0.5	14 (8.7%)	53 (55.2 %)	41 (77.4%)	20 (95.3%)	
Community & Affair					≈ 0
0	158 (98.1%)	80 (83.3%)	31 (58.5%)	4 (19.0%)	
≥ 0.5	3 (1.9%)	16 (16.7%)	22 (41.5%)	17 (81%)	
Home & Hobby					≈ 0
0	159 (98.8%)	69 (71.9%)	22 (41.5%)	3 (14.3%)	
≥ 0.5	2 (1.2%)	27 (28.1%)	31 (58.5%)	18 (85.7%)	
Personal Care					2E-03
0	161 (100%)	95 (99.0%)	50 (94.3%)	19 (90.5%)	
≥ 0.5	0 (0.0%)	1 (1.0%)	3 (5.7%)	2 (9.5%)	
CDR-GS					≈ 0
0	117 (72.7%)	10 (10.4%)	4 (7.5%)	0 (0.0%)	
≥ 0.5	44 (27.3%)	86 (89.6%)	49 (92.5%)	21 (100%)	

Table 2: Percentage distribution of normal vs impaired subjects at the baseline visit for each CDR domain in the identified clusters.

difference from the baseline throughout the entire follow-up period. Similar findings were observed within the Home & Hobby domain, except for *Cluster 3* and *Cluster 4* during Visit 2. In the Personal Care domain, *Cluster 1* and *Cluster 2* do not show statistical differences. Their values are almost similar during the follow-up period, as illustrated in Fig.1. On the contrary, *Cluster 1* is statistically different from *Cluster 3* and *Cluster 4* for all visits. *Cluster 2* differs from *Cluster 3* at all visits except at the baseline and Visit 3, while it differs from *Cluster 4* at all visits, with differences becoming more statistically significant from Visit 3 onward. Regarding Orientation, *Cluster 1* and *Cluster 2* show statistically significant differences from all other clusters for all visits starting from the baseline. The differences in Orientation of *Cluster 3* and *Cluster 4* at baseline and the first follow-up visit were not statistically different, thus giving evidence that individuals who will show a decline have similar orientation problems at the first visits. Starting from the third visit, the difference between the two clusters becomes more evident. Also, for the Judgment domain, *Cluster 1* is statistically different from all other clusters for all visits starting from the baseline, as well as *Cluster 2*. *Cluster 3* and *Cluster 4* do not statistically differ until the third follow-up visit, so the difference between the two clusters becomes statistically significant only at the fourth follow-up visit, i.e., when the decline is already occurring.

Regarding *Cluster 3*, at the baseline visit, the difference with *Cluster 4* is significant since *Cluster 4* includes subjects that, from the beginning, show an overall cognitive decline, showing impairment in all CDR domains except for Personal Care, which is not the case for patients in Cluster 3. At the follow-up visits, subjects of Cluster 3 start progressing in decline, so their memory impairment becomes more similar to the one experienced by patients of Cluster 4. However, the subjects of Cluster 4 became AD, so at the last follow-up visit, the two clusters were statistically different again in the memory domain.

Since our objective was to stratify progressive and nonprogressive patients to individuate factors that could be predictive of progression, Cluster 2 and Cluster 3 should be carefully analyzed since they include patients who can both progress or remain stable starting at the baseline visit, with a comparable percentage of memory-impaired patients

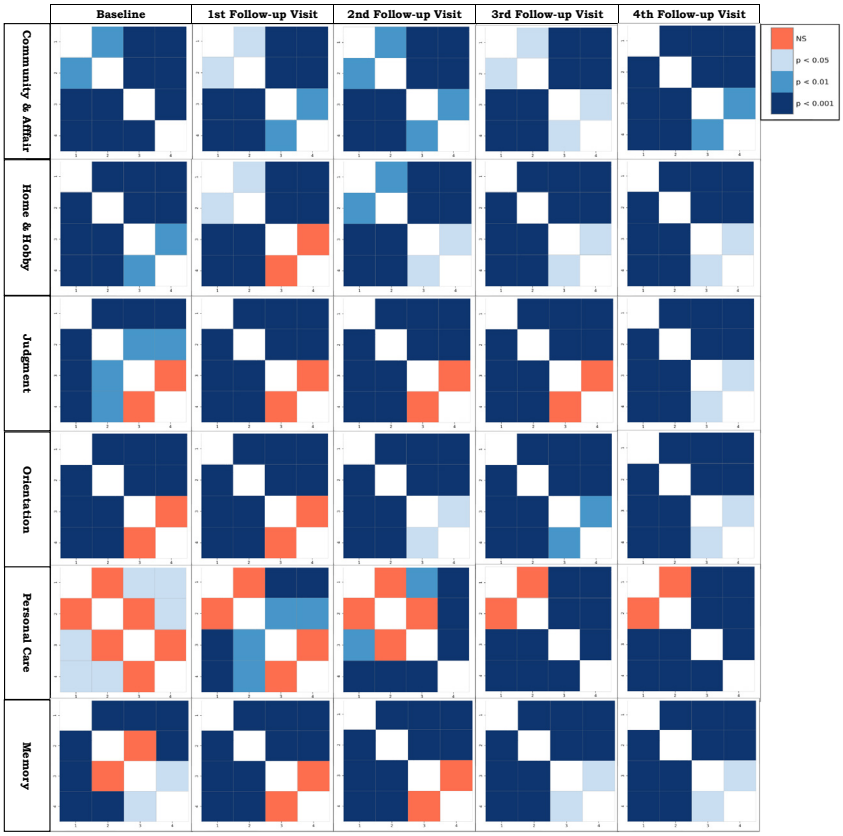


Fig. 4: Significance plots of CDR domains during the whole follow-up period

(see table 2). The differences between Cluster 2 and Cluster 3 are evaluated by considering the difference in percentage between the corresponding subjects for each domain, i.e., normal showing values = 0 and impaired showing values ≥ 0. This analysis shows that the main differences between Cluster 2 and Cluster 3 concern all CDR domains except Personal Care and Memory. However, among the remaining CDR domains, we do not consider as possible predictors the ones whose values rely mainly on the answers reported by the caregivers, i.e., Community & Affair and Home & Hobby, since in such cases, there is a heavy dependence on other factors, such as the social state of the patient family, and the profile and attitude of the caregiver, that may lead to a not objective evaluation of such CDR domains. So, we focus on the ones relying on direct interviews with subjects, i.e., Orientation and Judgment, for which Cluster 2 overcomes Cluster 3 by 31.1% and 22.2%, respectively. By performing a ϕ_K correlation analysis on these factors within Cluster 2 and Cluster 3, it results that for Cluster 2 the correlation index between Orientation and Judgment is 0.20 with a significance score of 2.91 (i.e., $pvalue < 0.05$), while for Cluster 3 this correlation index is 0.59 with a significance score of 1.89 (i.e., $pvalue < 0.05$), so the correlation is higher than the one of Cluster 2. The correlation between Orientation and Judgment from Cluster 2 to Cluster 3, together with the statistical significance difference between the clusters in these domains, is an encouraging result in concluding that Orientation and Judgment can be the most indicative factors of disease progression to discriminate among stable and progressive amnestic MCI patients.

4. Conclusions

The early detection of AD progression is crucial for administering prevention interventions to limit the decline of amnestic MCI patients. In this context, identifying prognostic factors of the AD disease plays a fundamental role in its prevention. Nevertheless, the possibility of relying on non-invasive medical assessments can be valuable for

fragile individuals. For this reason, we evaluated the prognostic value of CDR domains in predicting the progression of AD applying unsupervised longitudinal clustering over a 5-year follow-up period in an elderly cohort. Our findings help identify risk factors for the disease progression. In particular, it emerged that impairments in Orientation and Judgment at baseline are primarily associated with the progression to AD throughout the follow-up period among stable and progressor amnestic MCI patients. We plan to conduct further analysis on the same data set by including other neuropsychiatric factors to evaluate their correlations with the CDR domains considered in this work.

Acknowledgments

This paper was developed within the project funded by Next Generation EU – "Age-It – Ageing well in an ageing society" project (PE0000015), National Recovery and Resilience Plan (NRRP) – PE8 – Mission 4, C2, Intervention 1.3.

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