Identifying Dementia Subtypes with Electronic Health Records

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1 INTRODUCTION

Dementia is defined by a decline in memory and thinking that is significant enough to impair function in activities of daily living. Dementia has numerous causes, including reversible causes, such as medication-induced cognitive dysfunction, as well as irreversible causes, such as progressive neuro-degenerative disorders [3]. Alzheimer Disease (AD) is the most common cause of dementia in older adults, but many other disorders can cause or contribute to dementia, including cerebrovascular disease and diseases associated with Lewy bodies, tau tangles, or TARDNA-binding protein43 (TDP-43) [27]. Patients present with a variety of different symptoms and progress at different rates, which may be related to the underlying brain pathologies, variation in baseline cognitive ability, genetic background, medical comorbidities, and social determinants of health [18]. Hence, patients seen in a dementia clinic are highly heterogeneous and represent many different types of dementia. Better characterizing
Previous studies have used a priori-defined neuropathological categories to identify subtypes within a clinical dementia population [6, 8, 13]. However, these approaches define subtypes of pathologies based on clinical diagnosis, which rely on a "clinical intuition" instead of unbiased data-driven approaches [14, 15]. More recently, the increasing availability of Electronic Health Records (EHR) data combined with complex machine learning algorithms have encouraged data-driven approaches to identify patterns in clinical data [7]. These new data sources and methods may offer new insights into the underlying heterogeneity of dementia. For example, clustering algorithms can stratify dementia patients into subtypes based on key features recorded in the EHR that can enhance predictive ability compared to analyzing the entire cohort as a single homogeneous group [24].

There has been significant research which uses clustering techniques on EHR data to identify dementia subtypes. In [26], hierarchical clustering was applied on clinical data from a multi-speciality urban medical centre to identify multiple sub-phenotypes of Alzheimer Disease and related dementia. Another study applied a representation learning model on Mount Sinai Health system data and identified subtypes with variable degree of dementia symptoms [9]. Other studies focusing on dementia subtyping used 2 categories of structured clinical data sources as key features: brain atrophy patterns as measured by structural MRI [2, 4, 11, 16, 23] and cognitive impairment as measured by performance on cognitive tasks [1, 17, 19, 20, 25]. While most of these studies focus on identifying subtypes within a dementia cohort, little research has been done on interpreting the cognitive characteristics of the identified subtypes and how they are related to disease progression.

In this work, we use an unsupervised data-driven clustering approach to identify dementia subtypes. Our goal is to analyze if the identified subtypes have a logical relationship to each other based on our clinical understanding and knowledge. In contrary to prior work, our work focuses on both the interpretation of the identified subtypes based on domain knowledge and analyzing how the subtypes play a role in the longitudinal progression trajectory.
of the disease. Understanding the cognitive profile of the subtypes can lead to effective clinical decision-making and precision diagnostics tailored to each subtype. Our contributions can be summarized as follows (visual representation of the pipeline shown in Figure 1):

- Applying unsupervised clustering techniques on cognitive assessment scores to identify subtypes within a clinical dementia cohort.
- Interpretation of the identified subtypes in terms of their cognitive characteristics.
- Analyze transitions between the different subtypes and how they are related to disease progression.

Table 1. Demographic characteristics of our selected cohort (N = 1845 patients). All feature variables were calculated at the baseline visit of each patient.

| Feature variables (baseline) |          |
|-----------------------------|----------|
| Age (mean, SD)              | 73.2 years (11.9 years) |
| Female (n, %)               | 1038 (57%) |
| Race (n, %)                 |          |
| -White                      | 1605 (88.9%) |
| -Black or African American  | 181 (10%) |
| -Asian                      | 20 (1.2%)  |
| Clinical Dementia Rating (Median, IQR) |          |
| -Memory                     | 1 (0.5, 1) |
| -Orientation                | 0.5 (0, 1) |
| -Judgement and Problem Solving | 0.5 (0, 1) |
| -Community Affairs          | 0.5 (0, 1) |
| -Home and Hobbies           | 0.5 (0, 1) |
| -Personal Care              | 0 (0, 1)   |
| Cognitive Characteristics (Median, IQR) |          |
| -Mini-Mental State Exam     | 23 (19, 27) |
| -Boston Naming Test         | 14 (12, 15) |
| -Short Blessed              | 10 (2, 16) |
| -Verbal Fluency             | 12 (9, 16) |
| -Word List Recall           | 2 (1, 5)   |
| -Word List Memory Task      | 13 (10, 16) |
| Most Common Diagnoses (n, %) |            |
| -Memory Loss                | 1010 (19.6%) |
| -Alzheimer Disease          | 1075 (9.8%) |
| -Parkinsonism               | 66 (0.7%)  |
| -Major Depressive Disorder  | 466 (2.9%) |
| -Obstructive Sleep Apnea    | 374 (2.6%) |
2 METHODS
2.1 Data sources and study participants
Clinical data corresponding to office visits were extracted from the Electronic Health Records (EHR) of patients treated between June 2012 and May 2018 at the Memory Diagnostic Centre (MDC) at the Washington University School of Medicine in St. Louis, a large, academic, tertiary-care referral centre. All patients seen in the clinic were presented for evaluation of memory and/or thinking concerns. Patients underwent a comprehensive history, neurological examination, brief cognitive testing, and if indicated, laboratory testing and brain imaging. Patients were evaluated using the well-validated and widely used Clinical Dementia Rating (CDR®) at each visit, a five-point scale to characterize six different domains of cognitive and functional performance: memory, orientation, judgement and problem solving, home and hobbies, community affairs, and personal care [12]. For both the CDR global score and component scores, 0 denotes cognitively normal, 0.5 very mild dementia, 1 mild dementia, 2 moderate dementia and 3 severe dementia. Longitudinal data from 1,845 patients with 2,737 visits were eligible for inclusion, where each visit had a CDR score. Table 1 represents the baseline demographic characteristics of the selected cohort. This study was approved by the Washington University in St. Louis Institutional Review Board.

2.2 Feature selection for clustering analysis
Our initial set of feature variables consisted of cognitive assessment scores, indicating performance on a standardized battery of cognitive tasks to assess the severity of dementia. Compared to expensive and/or invasive procedures like neuroimaging biomarkers, these scores are standard metrics in dementia research and is recorded for all patients in the memory clinic. Next, we performed feature selection to determine the optimal set of features for clustering. We started with two sets of features as follows: (i) Cognitive assessment scores: Boston Naming Test, Mini-Mental State Exam, Short Blessed, Verbal Fluency, Word List Memory Task and Word List Recall, (ii) six components of CDR score: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The motivation behind choosing the individual CDR component as features compared to the aggregate Global CDR score is the fact that for patients having the same CDR score, the individual components might be different from one another, allowing us a more granular approach of studying the sub-phenotyping of patients.

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Fig. 2. The 2D T-SNE representations of the data for each of the 2 feature categories: cognitive scores only as features (left) and CDR components only as features (right). Each points represents a visit with the colour indicating the Global CDR score.
For each of the categories, we plotted the t-distributed stochastic neighbour embedding (T-SNE) distribution. Figure 2 shows the T-SNE 2-dimensional representations of each of the 2 feature sets across the CDR categories. We can see that using the cognitive scores as features creates a gradient from low to high CDR but did not result in clusters. On the other hand, using the CDR components as features created clusters that were distinct without any significant overlap across the CDR categories. Analyzing the degree of overlap of points across the different CDR categories, the six components of CDR were selected as the optimal set of features for clustering. Since each of the selected features are ordinal variables and had a very low missing rate of <5%, we followed the strategy in [28] and imputed the missing values for each feature column using the median value of that feature across all the 2737 visits.

2.3 Clustering method

In this study, we used the K-means clustering algorithm to generate the dementia subtypes. In K-means, the a priori-specified k number of clusters are identified through iteratively minimizing the distance between data points and their assigned cluster means [10]. We used the t-distributed stochastic neighbour embedding (T-SNE) [22] as a dimensionality reduction method prior to clustering. T-SNE lowers the dimension of the data while representing points in a geometrical space, thus transforming the data into a form where K-means can be applied.

One important issue is that the clustering analysis was performed on all data that was available from a 6-year period between 2012-2018, and some patients had multiple visits during this period. For the clustering step, each visit was assumed independent without any temporality (linkage) between individual visits of the same patient. The temporality information between individual visits was used downstream for analyzing the relationship between different clusters. This approach – including all visits for the clustering analysis as opposed to including the baseline visit of each patient was taken to enable downstream longitudinal analysis and track the symptom progression rate among patients. For example, at any given point in time, a patient exists in a single cluster (dementia subtype), but transitions between different clusters over time. The gap statistics algorithm [21] was used for determining the optimal number of clusters (K).

To gain an insight into which patients have a higher probability of progression, patient transitions between different dementia subtypes were analyzed across multiple visits. Patients with only a single visit were censored from our analysis. All the identified subtypes were characterized in terms of their cognitive characteristics. Finally, the differences in progression rate, both within and between Global CDR score categories were measured.

3 RESULTS

3.1 Clustering results

Figure 3 shows the gap statistics (left) and the clustering results (right). The gap statistic is used for determining the number of significant components, which was determined by the largest relative gap jump. From the gap statistic plot, K = 9, 11 and 16 were identified with significant relative gap jump compared to the other values of K (Figure 3). In line with the T-SNE distribution of CDR component scores across the CDR categories in Figure 2, the final K value was selected as 16. Comparing both the T-SNE and the clustering plots in Figure 2 (left) and Figure 3 (right) respectively, we can observe that the points with CDR = 0.5 are quite scattered and multiple clusters have been formed from them. This validates our hypothesis that dementia patients are quite heterogeneous, even within a single Global CDR level.

Figure 4 shows the CDR composition of each dementia subtype ordered by increasing CDR score (more severe dementia). Subtypes can either be homogenous, having a unique Global CDR or composite, including two Global CDR scores. We can observe that there is greater variability in early dementia (CDR of 0.5 or 1) leading to more dementia subtypes with a lower CDR score, compared to the more advanced dementia (CDR = 2 and 3). The
Fig. 3. The gap statistics results (left) and the clustering results using CDR component score as features (right). From the gap statistic plot, $K = 9, 11$ and 16 were identified with significant relative gap jump compared to the other values of $K$. We selected $K=16$ as the optimal number of clusters. The points in cyan (right) represent the centroids of each of the identified clusters. Each point represents an individual visit.

The above finding can also be confirmed from the T-SNE plot in Figure 2, where data points with CDR = 0.5 and 1 are more scattered, potentially forming multiple clusters (dementia subtypes).

Fig. 4. Stacked bar plot showing the CDR composition of each dementia subtypes ordered by increasing CDR score (dementia severity increases moving from left to right). The x-axis shows the 16 dementia subtypes and the y-axis represents the number of visits within each dementia subtypes. Some dementia subtypes included a unique Global CDR (e.g. $C_1$, $C_{13}$), while other dementia subtypes included two Global CDR scores (e.g. $C_{10}$, $C_{15}$).
3.2 Cognitive profile of identified subgroups
The association between the six CDR components and the dementia subtype allows interpretation of the cognitive profile of the subtypes. Figure 5 shows how each of the six components of CDR score vary across the 16 dementia subtypes. The individual component scores vary from 0-3 (0, 0.5, 1, 2, 3), with 0 indicating normal cognition and 3 indicating maximum impairment. For all the 6 CDR components, there was a natural transition of increasing cognitive impairment from the early (mild) to later (moderate to severe) stages of dementia. In this section, we analyzed 2 types of variability: (i) inter-subtype variability, which indicates the variability amongst dementia subtypes for a particular component score even with the same CDR and (ii) intra-subtype variability which indicates the variation in the 6 component scores within a particular dementia subtype.

3.2.1 Inter-subgroup variability. We evaluated the 6 dementia subtypes that only included patients rated CDR 0.5 (C1, C6, C7, C9, C13, C14), based on our observation in Figure 2 and 3 that the visits with CDR = 0.5 have the maximum underlying heterogeneity. C6 has a consistent memory score of 1 and has more impaired memory loss compared to the remaining 5 dementia subtypes with a mean memory score of 0.5. Similarly, C7 and C9 have fully healthy orientation while all the visits in C10 have moderate difficulty with their orientation. Compared to the remaining 5 dementia subtypes, C9 have relatively healthy judgement in solving daily activities. Patient visits in C9 and C14 are fully capable of community affairs with well-maintained home and hobbies, compared to the remaining dementia subtypes with relatively impaired performance in these 2 CDR component categories. Unlike the remaining 5 CDR components, personal care had no zero inter-subtype variability with all visits with CDR = 0.5 being fully capable of self-care without any kind of impairment. Dementia subtypes with greater than or equal to mild dementia stages (CDR = 1, 2, 3) had less cognitive variability than subtypes with CDR = 0.5 as observed from Figure 5.

3.2.2 Intra-subgroup variability. Next we examined how visits in the same dementia subtype can have variable CDR component distribution with respect to the 6 components of CDR. For example, patient visits in C9 have mild memory impairment, but are otherwise fully functional in the other domains. Patient visits in C14 have slightly impaired memory, orientation and problem-solving skills, but are otherwise healthy in personal care, community affairs and home and hobbies. Similarly, we can define the cognitive profile of each dementia subtype, which in turn captures the role of each of the 6 CDR components in capturing the heterogeneity within dementia patients. Analyzing the intra-subtype variability of all the dementia subtypes, we can conclude that memory, orientation and home and hobbies have a significant role in capturing the variability within the CDR = 0.5 groups. On the other hand, the personal care scores do not provide any significant insights.

3.3 Comorbidity characteristics of identified subgroups
We also analyzed the comorbidity profile of each of the 16 identified dementia subtypes. We identified the top 5 comorbid conditions of dementia patients in our dataset, which were Alzheimer Disease (AD), Major Depressive Disorder (depression), Memory Loss (not otherwise specified), Parkinson Disease and Obstructive Sleep Apnea (sleep disorder). Figure 6 shows the distribution of visits within each dementia subtype having the above 5 comorbid conditions. One important trend that we can observe is that the proportion of visits having AD is higher in the later stages of dementia (CDR = 1, 2, 3) compared to the early stage groups (CDR = 0.5). This observation shows that AD, the most common form of dementia, is more likely to be diagnosed in patients with more significant cognitive and functional impairment. On the other hand, the visits in early stage dementia subtypes (CDR = 0.5) are mostly characterized by a diagnosis of memory loss, depression and sleep disorders.
3.4 Disease progression through subgroup transitions

We next examined how patients transitioned between the different dementia subtypes over time and how these transitions were related to dementia progression. The units of each subtype are patient visits and a patient can exist in a single subtype at any given point in time, but can transition to the same or different subtype in their next visit. Since there are 16 subtypes and it is difficult to interpret the transitions between every pair of subtypes, we grouped the 16 subtypes into 6 broader categories $G_0 - G_5$ ordered as shown in Table 2. The subtypes were grouped based on if they represent a unique Global CDR score (homogenous) or two Global CDR (composite) and also in terms of increasing Global CDR from 0 to 3. For example, $G_0$ represents mostly the CDR = 0 visits while $G_1$ has all the subtypes with CDR = 0.5, corresponding the homogenous orange bars in Figure 4.

Table 3 shows the number of transitions between every pair of dementia subtype groups. For example, the 170 transitions between $G_1 \rightarrow G_1$ signifies that there are 170 instances where a particular patient that was in $G_1$ (CDR = 0.5) remained in $G_1$ (CDR = 0.5) at their next visit. The transitions involving definite change in CDR include both progression to higher CDR score (e.g. $G_1 \rightarrow G_3$) and regression to a lower CDR score (e.g. $G_4 \rightarrow G_1$). The regressions signify that there are some dementia patients whose cognitive conditions improved in their next visit. While regression is not common, it is important to identify these patients and investigate the reasons for their
cognitive improvement. From Table 3, we can observe that 2 patients progressed from $G_0 \rightarrow G_5$ and $G_1 \rightarrow G_5$ respectively, moving from CDR = 0.5 to CDR = 2, 3 at their next visit and skipping the intermediate CDR = 1 stage, suggesting either rapid progression or a long follow-up interval between visits. On further introspection, we found that the patient moving from $G_0 \rightarrow G_5$ had a short follow-up length (interval between successive visits) of 184 days while the patient moving from $G_1 \rightarrow G_5$ had a long follow-up length of 679 days. While the former observation indicates chances of actual rapid progression, the latter signifies that the probable reason of CDR jump is long follow-up of that patient.

Next, we examine how the dementia subtype group transitions shown above can be related to dementia progression. Figure 7 shows the transitions from CDR = 0.5 to higher CDR score of 1, 2 and 3. Out of all the CDR 0.5 visits, individuals classified into dementia subtype $C_{10}$ and $C_{13}$ had the highest progression to CDR = 1 at their next visit. On the contrary, dementia subtypes like $C_7$ rarely progressed to higher CDR stages. This observation validates our hypothesis that individuals rated CDR = 0.5 are highly heterogeneous and have a variable rate of dementia progression.
Table 3. Number of transitions between every pair of dementia subtype groups. The subtype groups in header column (Start) and header row (End) represent source and target respectively.

| Start/End | $G_0$ | $G_1$ | $G_2$ | $G_3$ | $G_4$ | $G_5$ |
|-----------|-------|-------|-------|-------|-------|-------|
| $G_0$     | 36    | 15    | 1     | 0     | 0     | 1     |
| $G_1$     | 17    | 170   | 47    | 55    | 13    | 1     |
| $G_2$     | 1     | 19    | 44    | 66    | 24    | 10    |
| $G_3$     | 0     | 5     | 10    | 74    | 51    | 20    |
| $G_4$     | 0     | 2     | 4     | 9     | 62    | 45    |
| $G_5$     | 0     | 0     | 0     | 1     | 10    | 79    |

**Transitions**: CDR = 0.5 $\rightarrow$ 1, 2, 3

Fig. 7. Graph showing transitions which are related to progression from CDR = 0.5 to higher CDR values 1, 2 and 3. The yellow and green nodes in the graph represent the subtypes with CDR = 0.5 and CDR = 1 visits respectively. For $C_{15}$, which has 2 CDR (0.5/1), we only considered the visits with CDR = 1. The edge weights represent the number of transitions from source to target. For example, edge weight of 4 between $C_{10} \rightarrow C_{15}$ means that there are 4 instances where patients were in $C_{10}$ in the current visit and in $C_{15}$ in their next visit. Only the transitions with edge weights $\geq 4$ are shown here.

4 DISCUSSION

The goal of our study was to apply an unsupervised data-driven clustering approach to identify dementia subtypes within a specialty dementia clinic. We extracted outpatient office visits from an EHR, selected the 6 components of CDR as the optimal set of features after a feature selection step, and applied the K-means algorithm to identify 16 dementia subtypes. In contrast to prior work, our work focuses on both the interpretation of the identified
subtypes based on their cognitive characteristics and analyzing how the subtypes play a role in the longitudinal progression trajectory of the disease.

4.1 Clustering on individual visits
In this work, the unsupervised clustering analysis was performed with data from individual visits, rather than each patient, which assumed that each visit of the same patient is independent without any longitudinal relations between the consecutive visit. Our goal was to blind ourselves to the temporality (linkages) between visits, and later utilize the temporal aspect to investigate the relationship between the clusters (dementia subtypes). First, dementia often progresses over a decade, whereas our window of EHR data is a maximum of six years. Rigorous analysis of longitudinal data is only possible when information about all the visits of a particular dementia patient is available, and in this dataset, we are evaluating a cross-section of data from patients that encompasses different windows of their clinical care (e.g. some may have been seen in 2006-2014, others from 2016-2022). Since we had EHR data from 2012-2018 only, we decided to perform the clustering at the visit level. This approach also helps in increasing the volume of data available for clustering, since we had only 1845 patients in our dataset who satisfied the eligibility criteria. Since the units of each dementia subtype are individual visits and not patients, a patient can have the first visit in one dementia subtype and the next visit in the same or a different subtype. This approach not only allows us to analyze the relationship between dementia subtypes but also the differential progression trajectory of dementia patients. Although our experimental analyzes have been demonstrated in terms of dementia subtypes, our findings could be made more granular by focusing on the heterogeneity of individual patients. For example, when we say a particular dementia subtype with CDR = 0.5 has a higher chance of progression to CDR = 1, 2, 3 compared to the other subtypes, we can investigate the patients who have visits in that particular subtype and track their remaining visits across all subtypes. We believe that this visit-level approach is more robust and generalizable in terms of investigating heterogeneity and disease progression compared to the patient-level approach of clustering using only the baseline information of each dementia patient.

4.2 Prioritizing early stage dementia subgroups for precision diagnostics
In our analysis, we focused our attention on the visits with CDR = 0.5 to investigate the level of heterogeneity. From our observation in Figures 2-5, we can conclude very mild dementia (CDR = 0.5) is much more heterogeneous than more severe dementia. We defined the cognitive profile of each dementia subtype and examined both the inter-subtype and intra-subtype variability. For example, individuals in the same dementia subtype can have different scores in memory, orientation, judgement and problem solving and community affairs (intra-subtype variability). We also evaluated the variability amongst dementia subtypes in their performance on the individual component tasks for CDR. In Figure 5, we can see that the dementia subtypes with more severe dementia (CDR = 1, 2, 3) have worse performance on CDR component tasks with lower variability. Improved classification of individuals with very mild dementia may enable more accurate diagnosis and prognosis, which may also be helpful in weighing the potential benefits of certain treatments. For example, if a patient is very likely to progress to more severe dementia, a treatment with significant risks may have greater justification.

4.3 Variability in CDR progression
In Table 3, we observed two interesting patterns in terms of CDR progression: (i) regression in CDR global score, signifying that some patients improve and (ii) skipping CDR stages during progression, where a patient can skip a CDR stage during progression (e.g. move directly from CDR = 0.5 to 2 in their next visit). The regression in CDR score could be related to treatment of conditions that can cause or worsen dementia symptoms. For example, dementia specialists often discontinue medications that impair cognition, and patients often improve after these
changes are made. Skipping CDR stages during progression could be related to actual rapid progression or a long interval between adjacent visits. Events like a stroke or a fall can significantly worsen the cognitive abilities of a patient, increasing the apparent rate of progression. Changes in the collateral source (caregiver, family member) who accompanies the patient in his/her follow-up visit and informs the clinician of the patient’s condition can affect the CDR. This reflects a potential bias in the clinical rating of dementia.

4.4 Limitations and scope for future work

One of the limitations is the fact that we have tested our approach on a single EHR dataset. As part of future work, we plan to test the generalizability of our pipeline on additional datasets. Another limitation is the relatively small sample size of our dataset which restricts our ability to perform rigorous statistical analyzes on the variable rate of progression of dementia subtypes. The main motivation behind our analysis was to analyze the initial patterns of heterogeneity seen within a dementia cohort and possible solution of parsing the heterogeneity by characterizing the dementia subtypes. Applying this pipeline to a larger EHR dataset can allow us to estimate probabilistic estimates of disease progression, backed by rigorous statistical analysis.

5 CONCLUSION

In this research, we applied an unsupervised data-driven clustering approach to EHR data from a dementia specialty clinic to identify dementia subtypes based on CDR component scores. Our goal was to characterize the cognitive profile of the dementia subtypes and analyze how the subtypes change over time. We observed that dementia subtypes that represented individuals with very mild dementia (CDR 0.5) had widely varying rates of transition to other subtypes. Future work includes testing the generalizability of our proposed pipeline on additional datasets, and using a larger volume of EHR data to estimate probabilistic estimates of the variability between dementia subtypes both in terms of cognitive profile and disease progression.

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