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Distribution of neuropsychiatric profiles and comorbid diseases in dementia subtypes

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ABSTRACT

Objectives: Alzheimer's disease (AH) is the most prevalent cause of dementia, followed closely by vascular dementia. Mixed vascular-Alzheimer's dementia (MVAD) is more evident in individuals aged 80 and above. Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia after AH. Vascular risk factors play important role in the pathogenesis of dementia syndromes. Behavioral and psychological symptoms represent a significant portion of the non-cognitive manifestations in dementia patients. This study aimed to evaluate the distribution of chronic diseases, behavioral disorders, psychiatric findings, and medication use in patients followed with different dementia diagnoses.

Methods: Prevalance of chronic diseases, behavioral disorders, psychiatric findings as well as the usage of antidepressant and antipsychotic medications among patients followed up in dementia outpatient clinics with the diagnosis of AD, mild cognitive impairment (MCI), vascular dementia (VaD), FTD, and MVAD were investigated. Neuropsychiatric inventory (NPI) was applied to the patients.

Results: Four hundred and fifty-five patients were accepted in the study. The patients were distributed as follows: AD (n=303, female/male: 187/115, age = 78±8 years), MCI (n=53, female/male: 31/22, age = 69±10 years), VaD (n=31, female/male: 18/13, age = 68±9 years), FTD (n=32, female/male: 17/15, age = 68±9 years), and MVAD (n=36, female/male: 16/20, age = 76±10 years). Both AD and MVAD groups were significantly older than the other groups (F = 23.2, P<0.0001). The ratio of comorbid chronic diseases was 80% in the AD group, 72% in the MCI group, 91% in the VaD group, 59% in the FTD group, and 93% in the MVAD group. In the whole group, antipsychotic drug use was 27.5% and antidepressant drug use was 28.9%. The mean NPI

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score was 32.9±28 in antipsychotic users and 16±19 in non-users (P<0.0001). The mean NPI of antidepressant users was 17.6±19 and 21.9±25 (P=0.055) in non-users.
Conclusion: There is a comorbid chronic disease burden in all dementia subtypes, although at varying intensities, and as the chronic disease burden increases, behavioral disorders and psychotic findings increase, and accordingly, the use of antipsychotics also increases.
Keywords: Dementia, chronic disease, behavioral disorders, antidepressants, antipsychotic

Dementia is a rapidly growing global health concern, particularly affecting individuals aged 65 and older. Alzheimer's disease (AD) stands as the most prevalent cause of dementia, followed closely by vascular dementia (VaD) [1]. Notably, the occurrence of mixed vascular-Alzheimer's dementia (MVAD) has exhibited a rising trend, becoming more evident in individuals aged 80 and above, with prevalence climbing from an average of 25% to 35%. The autopsies performed on individuals over the age of 85 with mixed vascular-Alzheimer's dementia have revealed distinctive brain changes characterized by astrogliopathy, synucleinopathy, and TDP43 protein aggregation [2]. Frontotemporal dementia (FTD) emerges as the second most common cause of early-onset dementia in individuals under the age of 65, ranking just behind AD [3]. Recent research indicates to the active role of vascular risk factors in various types of dementia, suggesting that most forms of dementia can be viewed as integral components of vascular disease [4].

Behavioral and psychological symptoms represent a significant portion of the non-cognitive manifestations in dementia patients. These symptoms not only contribute to heightened morbidity and burden on the caregivers but also lead to a decline in the quality of life for both the affected patient and their caregiver [5]. The spectrum of behavioral disorders associated with dementia includes anxiety, depression, irritability, psychomotor agitation, delusions, hallucinations, apathy, disinhibition, abnormal motor behaviors, and circadian rhythm disorders. The intensity and expression of these symptoms and disorders exhibit heterogeneity among patients and may vary over time. The presence of specific behavioral disorders within distinct subtypes of dementia remains a subject of debate in the field [5].

In our previous study, we investigated the neuropsychiatric effects of total and partial lockdown measures in 302 Alzheimer's patients who were followed up during the COVID-19 pandemic [6]. As a continuation of that study, this time we investigated the follow-up of dementia patients, the burden of comorbid chronic diseases, the distribution of behavioral and psychotic disorders, and the intensity of antidepressant and antipsychotic medication use by including other types of dementia as well as AD.

METHODS

This study involves a further follow-up of patients, who were followed in a multicenter study titled "Neuropsychiatric Effects of COVID-19 Pandemic on Alzheimer's Disease: A Comparative Study of Total and Partial Lockdown" [6] and is its continuation. The diagnoses are based on the criteria defined by DSM-IV (Diagnostic and statistical manual of mental disorders) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) for Alzheimer's Disease (AD), NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences) [7] for Vascular Dementia (VaD), and Petersen for mild cognitive impairment (MCI) [8].

All FTD patients were behavioral variants and were diagnosed according to the diagnostic criteria proposed by Rascovsky *et al*. [9]. MVAD was diagnosed according to the criteria of Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC). Even though MVAD is very similar to Alzheimer's disease, which is a primary amnestic syndrome, the cranial imaging shows cerebral vascular changes (leukoaraiosis, diffused white matter changes, lacunes) along with cognitive disorders [10].

The chronic diseases included in the study were hypertension, DM, chronic heart disease, chronic kidney disease, stroke, hypothyroidism, and cancer. For

chronic heart diseases, coronary heart disease and heart failure were included.

Neuropsychiatric inventory (NPI) was applied to the patients [11]. In addition, the total scores were considered for depression, anxiety, irritability, and agitation as neurotic symptoms; hallucinations and delusions as psychotic symptoms; and sleep and eating disorders as circadian rhythm disorders in the NPI. For the last category, apathy, euphoria, disinhibition and abnormal motor behaviors were considered in the total score of others [5]. The severity of dementia was assessed on the CDR (Clinical Dementia Rating) scale [12].

Statistical Analysis

For statistical analyses, SPSS version 16.0 (IBM, Chicago, IL, USA) was used. Demographic data was expressed as mean ± standard deviation and categorical data as percentage (%). A two-way ANOVA was used to analyze multiple groups, Pearson's correlation coefficient for correlation analysis, and Student's t-test for comparing the averages of two groups. LSD was used as post-hoc analysis in the ANOVA test. Multiple regression analysis was performed to determine the factors affecting NPI. Statistical significance value was accepted as $P<0.05$.

RESULTS

This study involved a further follow-up of dementia patients, who were followed after the COVID-19 pandemic in the previous study, as well as an investigation of the burden of comorbid chronic diseases, the distribution of behavioral and psychotic disorders, and the intensity of antidepressant and antipsychotic medication use.

This multicenter, cross-sectional study included 488 patients. After excluding 33 patients due to Parkinson's disease, dementia with Lewy bodies, normal pressure hydrocephalus, and Parkinson's disease dementia, 455 patients remained in the study. The patients were distributed as follows: AD (n=303, female/male: 187/115, age = 78±8 years), MCI (n=53, female/male: 31/22, age = 69±10 years), VaD (n=31, female/male: 18/13, age = 68±9 years), FTD (n=32, female/male: 17/15, age = 68±9 years), and MVAD (n=36, female/male: 16/20, age = 76±10 years). On average, both AD and MVAD groups were significantly older than the other groups ($F = 23.2$, $P<0.0001$). There was no statistically significant difference between the groups in terms of gender ($F = 0.97$, $P=0.41$). There was no statistically significant difference between the groups in terms of education level ($F = 0.91$, $P=0.45$).

In our study, 68% of the entire dementia group had hypertension, 24% had DM, 15% stroke, 28% heart disease, 1% cancer, 3% renal failure, and 2% hypothyroidism. The ratio of comorbid chronic diseases was 80% in the AD group, 72% in the MCI group, 91% in the VaD group, 59% in the FTD group, and 93% in the MVAD group. The lowest ratio of comorbid chronic

Table 1. Distribution of chronic diseases by different types of dementia

	AD	MCI	VaD	FTD	MVAD	F	Pvalue
Hypertension	68%	57%	78%	55%	79%	1.38	0.23
DM	24%	17%	30%	14%	39%	1.72	0.14
Heart failure	31%	13%	30%	23%	32%	1.91	0.10
Kidney failure	2%[a]	6%[a]	0%[a]	0%[a]	11%[b]	2.55	**0.03**
Stroke	9%[a]	4%[a]	78%[b]	9%[a]	57%[c]	43.4	**<0.0001**
Cancer	1%	2%	0%	0%	0%	0.28	0.88
COPD	5%	4%	4%	0%	4%	0.28	0.88
Hypothyroidism	3%	0%	0%	0%	4%	0.7	0.59

AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD=Vascular dementia, FTD=Frontotemporal dementia, MVAD=Mixed vascular-Alzheimer's dementia, DM=diabetes mellitus, COPD=chronic obstructive pulmonary disease, [a-c]There is no difference between groups with the same letter for each measure.

Table 2. Distribution of behavioral and psychiatric symptoms and medication use in different types of dementia

	AD	MCI	VaD	FTD	MVAD	F	P value
Antipsychotics	31%[a]	0%[b]	30%[a]	32%[a]	32%[a]	5.99	**<0.0001**
Antidepressants	26%[a]	26%[a]	44%[a,c]	32%[a,c]	50%[b,c]	2.49	**0.04**
Cholinesterase inhibitors	82%[a]	55%[b,c]	44%[b]	32%[b,c]	75%[a]	13.1	**<0.0001**
Glutamate antagonists	43%[a]	6%[b]	17% [b,c]	27%[a,b,c]	32%[a,c]	8.37	**<0.0001**
NPI	22±24[a]	6±7[b]	19±24 [a]	25±25[a]	22±24[a]	6.17	**<0.0001**
Neurotic symptoms	6.8±8[a]	3.2±4[b]	7.8±10[a]	8.6±11[a]	8.2±9[a]	2.97	**0.01**
Psychotic symptoms	3.8±5[a]	0.3±0.7[b]	3.6±6[a]	3.7±6[a]	5.2±6[a]	6.5	**<0.0001**
Circadian rhythm disorders	4.9±6[a]	1.6±3[b]	4.6±7[a,b]	4.9±5[a]	4.3±6[a,b]	2.64	**0.03**
Others	3.3±5[a]	0.2±0.6[b]	2.7±3[a]	6.3±5[c]	3.7±6[a]	6.9	**<0.0001**
NPI							
Antipsychotics (+)	32.6±28	-	46.2±29	18±16	37.8±27		
Antipsychotics (-)	18.3±20	6.1±7	8.1±9	28.2±29	15.8±19		
P value	**<0.0001**		**0.01**	0.39	**0.02**		
NPI							
Antidepressants (+)	19.4±18	9.6±10	13.6±24	27.4±34	13.2±11		
Antidepressants (-)	23.9±25	4.8±6	24.5±24	23.8±21	32.5±30		
P value	0.09	**0.04**	0.3	0.7	**0.04**		

AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD=Vascular dementia, FTD=Frontotemporal dementia, MVAD=Mixed vascular-Alzheimer's dementia, DM=diabetes mellitus, COPD=chronic obstructive pulmonary disease, NPI=neuropsychiatric inventory. Antipsychotics (+)=using antipsychotics, Antipsychotics (-)=not using; Antidepressants (+)=using antidepressants, Antidepressants (-)=not using. [a-d]There is no difference between groups with the same letter for each measure.

Table 3. Distribution of behavioral and psychiatric symptoms and ratios of medication use depending on the severity of dementia

CDR	0.5	1	2	3	F	P
N	149	171	83	52		
Antipsychotics	11%[a]	34% [b]	37%[b]	43%[b]	5.99	**<0.0001**
Antidepressants	34%	27%	22%	29%	2.49	0.33
Cholinesterase inhibitors	66%	76%	78%	77%	1.95	0.12
Glutamate antagonists	17%[a]	33%[b]	59%[c]	61%[c,d]	20.0	**<0.0001**
NPI	8±1[a]	22±25 [b]	26±23[b]	44±25[c]	35.6	**<0.0001**
Neurotic symptoms	4±5[a]	7.9±9 [b]	7.1±8[b]	9.6±8[b]	7.94	**<0.0001**
Psychotic symptoms	0.8±1[a]	3.8±5 [b]	5.2±5[c]	7.7±5[d]	31.2	**<0.0001**
Circadian rhythm disorders	1.9±3[a]	4.6±5 [b]	5.8±6[b]	11.4±8 [c]	24.8	**<0.0001**
Others	0.9±2[a]	3.5±6 [b]	4.5±5[b,c]	5.7±5 [c]	15.6	**<0.0001**

CDR=clinical dementia rating scale, NPI=neuropsychiatric inventory, [a-d]There is no difference between groups with the same letter for each measure.

Table 4. Correlation analysis between age and NPI scores in dementia types

	AD	MCI	VaD	FTD	MVAD
NPI/ Age	0.177	0.109	0.210	0.157	0.549
P value	**0.002**	0.43	0.33	0.48	**0.002**

NPI=neuropsychiatric inventory, AD=Alzheimer's disease, MCI=Mild cognitive impairment, VaD= Vascular dementia, FTD=Frontotemporal dementia, MVAD= Mixed Vascular-Alzheimer's Dementia

disease was in the FTD group (F = 3.19, P=0.01). When the distribution of chronic diseases in different types of dementia is examined, stroke in the VaD group and renal failure in the MVAD group were found to have a significantly higher rate than the other groups. (Table 1).

The numbers of chronic diseases were identified as 1.4±1 in AD, 1±0.8 in MCI, 2.2±1 in VaD, 1±1 in FTD, and 2±1 in the MVAD groups. A comparison of both VaD and MVAD groups with the other groups showed a statistically significant difference in the number of chronic diseases (F = 10.3, P<0.0001). In the whole group, antipsychotic drug use was 27.5% and antidepressant drug use was 28.9%. The mean NPI score was 32.9±28 in antipsychotic users and 16±19 in non-users (P<0.0001). The mean NPI of antidepressant users was 17.6±19 and 21.9±25 (P=0.055) in non-users. Table 2 shows the distribution of drug use and NPI symptoms in different types of dementia. There is no use of antipsychotics in MCI, but they are used in around 30% of other types of dementia. Antidepressant medications are most used in the MVAD type. This is followed by VaD and FTD dementia. No significant difference was detected between dementia types in posthoc analyses. Cholinesterase inhibitors are used most in AD and MVAD type dementia and least in FTD. Glutamate antagonists are least used in MCI. Average NPI scores are highest in FTD type and lowest in MCI type. Neurotic and psychotic symptoms, circadian rhythm disorders and other NPI symptoms were found to be significantly lower in MCI than in other dementia types (Table 2). In other types of dementia, except for FTD, NPI scores are higher in those who use antipsychotics than in those who do not use antipsychotics drugs. In the MCI and FTD groups, NPI scores of those using antidepressants were higher (Table 2).

The mean NPI score of patients with chronic diseases was 21.7±24 and 16.5±20 (P=0.06) in patients without chronic diseases. There was a positive corre-

Table 5. Regression analysis results of factors affecting NPI

	B	SD	β	P value
NPI	99.88	33.8		
Age	0.25	0.11	0.1	**0.028**
CDR	11.49	1.35	0.38	**0.0001**
Hypertension	1.73	2.32	0.033	0.45
Diabetes mellitus	-3.06	2.45	-0.055	0.21
Heart failure	-4.32	2.38	-0.082	0.07
Kidney failure	-9.54	6.30	-0.067	0.13
Stroke	-5.93	2.96	-0.089	**0.046**
Cancer	-20.51	9.54	-0.093	**0.032**
COMD	-11.69	5.14	-0.099	**0.023**
Hypothyroidism	-3.01	7.18	-0.018	0.67

SD=standard deviation, B=Unstandardized coefficient β=Standardized coefficient, CDR=Clinical Dementia Rating, NPI=neuropsychiatric inventory. Dependent variable: NPI R2=0.232

lation between the ages and NPI scores of the patients (r= 0.236, P<0.0001). Accordingly, as the number of chronic diseases increased, so did the NPI score (r= 0.143, P=0.003). A positive correlation was found between NPI score and CDR (r= 0.420, P<0.0001). In Table 3, antipsychotic use is lowest in the dementia group with CDR 0.5, and glutamate use is highest in the group with CDR 2 and 3. The highest NPI scores and subsections are in the group with CDR 3. In the correlation analysis of age and NPI in dementia types, a positive significant correlation was detected only in AD and MVAD type dementia (Table 4). In the regression analysis, the most effective parameters on NPI were determined to be age, CDR, stroke, cancer and COPD (Table 5).

DISCUSSION

This study focused on the distribution of chronic diseases, behavioral disorders, psychiatric findings and the prevalence of antipsychotic and antidepressant drug use in patients followed in dementia outpatient clinics with different dementia diagnoses.

It is reported that the burden of chronic disease is high in elderly individuals with dementia, with stroke found in 24% and coronary artery disease in 33%. Hypertension is a major risk factor for the brain, while depression, DM and coronary heart diseases have been reported to be more important factors in developing memory defects [13]. In our study, the highest rates of comorbid diseases were hypertension, heart diseases, diabetes mellitus and stroke. In terms of dementia types, the comorbid disease burden is found in MVAD, VaD, AD, MCI and FTD, respectively. Hypertension, heart failure, and DM were found to be at the highest ratios in the VaD and MVAD groups. A comparison among dementia types has shown that stroke was significantly higher in VaD and MVAD, while renal failure was significantly higher in MVAD. The prevalence of cognitive dysfunction in chronic kidney diseases has been reported as 16-38% [14]. It is suggested that this condition is caused by the accumulation of various endogenous and exogenous substances in the blood that are toxic to the brain, disruption of the blood-brain barrier, systemic inflammation, activation of NMDA receptors and oxidative stress [14]. In uremic animal models, pyknosis and apoptosis have been demonstrated in hippocampal neurons. Widespread white matter changes have been shown in 33% of patients with chronic renal failure, and these have been stated to cause cognitive effects [15]. In our study, a high rate of renal failure was detected in the MVAD group. The higher rate of kidney failure in the MVAD group than the other dementia groups may suggest more severe vascular involvement as well as the hippocampus.

Seventy percent of stroke survivors develop cognitive deficits depending on the type of stroke and level of disability. This may occur in patients with subarachnoid, intracerebral hemorrhages and ischemic stroke [16, 17].

Typically, cognitive deficits are known to appear 3-6 months after a stroke; however, some researchers define these as early- and late-onset cognitive deficits [18]. Irreversible cognitive impairments that appear within six months after a stroke are called “post-stroke dementia” [19]. No distinction is made between vascular cognitive impairment and post-stroke cognitive impairment, which are both addressed within the scope of vascular dementia [18]. Furthermore, risk factors such as hypertension, heart diseases and DM play a major role in vascular dementia [20]. According to the CogFAST study, the presence of three or more cardiovascular risk factors at advanced ages increases the risk of post-stroke dementia by 3.6 [21]. In our study, stroke was detected at a rate of 78% in VaD type dementia and 57% in MAVD type dementia. The number of chronic diseases is two or more in these two groups of dementia. AD and MVAD type dementias are seen at an older age than other dementias.

Some studies have suggested that the dementia subtypes do not present differences in terms of behavioral and psychological symptoms. The intensity of neuropsychiatric symptoms in dementia subtypes may fluctuate over time, and several factors, including various underlying neurobiological changes, comorbidities, pathologies in cerebral vascularization, and age play a role in such fluctuations [22]. In addition to cognitive loss, Alzheimer’s disease also presents symptoms such as behavioral changes, psychosis, mood swings, apathy, agitation, and abnormal motor behaviors [23]. Patients with vascular dementia demonstrate a specific neuropsychiatric pattern characterized by

depression with low response to antidepressants, as well as psychomotor decline, anxiety, apathy, and emotional withdrawal [10, 24].

In the behavioral variant of frontotemporal dementia, symptoms such as personality changes, disinhibition, inappropriate sexual behavior, and socially maladaptive behaviors are observed predominantly [25]. While disinhibition is the most prominent symptom, apathy is also a common early finding that may present in the form of loss of interest in social and non-social activities. Excessive alcohol intake and smoking, excessive consumption of sweets, hyperorality, and inappropriate behaviors may also be noted. FTD patients with C9ORF72 mutation may present psychotic symptoms such as visual and auditory hallucinations and delusions [26].

In our study, symptoms, including neurosis, psychosis, circadian rhythm disorders, and other behavioral disorders were observed in the lowest rates in the MCI group. Among these, neurosis and other behavioral disorders were the highest in FTD, psychotic behaviors the highest in MVAD, and circadian rhythm disorders the highest in AD and FTD groups. In terms of rating dementia, all behavioral disorders increased as did the CDR score. In our study group, behavioral disorders increased in direct correlation to the increase in age and chronic disease burden. An increase in neuropsychiatric symptoms with age has been observed, especially in AD and MVAD type dementias. In the regression analysis, age, CDR, stroke, cancer and COPD were determined as effective factors in neuropsychiatric symptoms.

The types and severity of psychiatric symptoms may vary throughout the course of dementia. Morbidity in patients leads to poorer quality of life, thus increasing the caregivers' burden [27].

Even though antipsychotics have side effects such as worsening morbidity and disability, they are still used to treat behavioral disorders in the natural course of dementia. Other undesirable side effects include decline in cognitive performance, falls, delirium, hypotension, and sedation as well as extrapyramidal side effects. In contrast, atypical antipsychotics tend to be safer and more tolerable medications [28].

A study conducted in 2015 in the UK reported that fewer than 50% of patients with dementia used antipsychotics [29]. It was further reported that 20% of dementia patients were prescribed antipsychotics to treat symptoms such as agitation, aggression, yelling, sleep disorders, behavioral symptoms, hallucinations, and delusions, with only one fourth of the patients benefiting from these medications [30]. In our study, approximately 30% of all dementia subtypes except for the MCI group were prescribed antipsychotics. When evaluated in terms of antipsychotics, NPI scores were found to be high in those using antipsychotics in the AD, VaD and MVAD groups. In the FTD group, NPI scores were higher in patients not using antipsychotics. We can explain this situation by being selective in the use of antipsychotics in dementia patients and mostly giving them to the patients with significant behavioral disorders and psychotic symptoms. We can attribute the higher NPI scores of FTD patients who do not use medication to the fact that the patients are non-compliant with treatment and their control is more difficult.

The effectiveness of antidepressants is also a highly debated topic. Some researchers defend that a positive response is achieved, while others argue that they are ineffective [31]. The effective dose range also varies [32]. Moreover, antidepressants may lead to increased risk of falls, higher mortality, and hospitalization in this age group [33]. Selective serotonin reuptake inhibitors (SSRIs) are the most common antidepressant group prescribed for these patients [34]. In our study group, antidepressants were used by 44% and 50% of the VAD and MVAD groups, respectively, 26% of the AD and MCI groups, and 32% of the FTD group. NPI scores were found to be higher in the AD, VaD and MVAD groups that did not use antidepressant medication. In the MCI and FTD groups, NPI scores were higher in those using antidepressant medication. We can explain this situation by the fact that antidepressant drugs are used less than necessary in the AD, VaD and MVAD groups.

In recent years, exercise therapy, light therapy, music therapy, and massage therapy are also recommended as non-pharmacologic approaches [35].

Limitations

The limitations of our study were the limited number of cases and the non-availability of individual depression and anxiety scales. Further studies are recommended by increasing the number of patients,

assessing the response to antidepressant and antipsychotic treatments, and evaluating the side effect profiles.

CONCLUSION

In conclusion, all dementia subtypes come with a comorbid chronic disease burden in varying intensities, and behavioral disorders and psychotic findings increase as does the chronic disease burden. While the behavioral disorders and psychiatric symptoms coexisting with dementia types do not present a very specific pattern, depression, anxiety, irritability, and agitation were observed prominently in FTD and MVAD; the circadian rhythm disorders, which include sleep and eating disorders, were observed significantly in AD and FTD; hallucinations and delusions were seen in MVAD; and apathy, euphoria, disinhibition, and abnormal motor behaviors, included in others, were noted significantly in FTD. Even though antipsychotics were prescribed for 30% of all dementia subtypes, except for FTD, antidepressants were used more intensively, particularly in VAD and MVAD. It has been observed that age, CDR and chronic diseases, especially stroke, cancer and chronic obstructive pulmonary diseases, are effective on neuropsychiatric findings. Detection and effective treatment of chronic diseases are at least as important as medications in controlling neuropsychiatric findings and should be handled carefully.

Ethics Committee Approval

This study was approved by the clinical research ethics committee of Maltepe University Faculty of Medicine Ethics Committee Date: (2020/900/54).

Authors' Contribution

Study Conception: SK, NGB; Study Design: SK, NGB; Supervision: SK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SK, NGB, NÇ, MFA, ŞŞ, FSK, ÖGÖ, TO, FE, DYO, ÖT, MKG, EAD, ZY, HE, BSAP, NE, EKT, ÖA; Statistical Analysis and/or Data Interpretation: SK, ŞŞ; Literature Review: SK, NGB; Manuscript Preparation: SK, NGB and Critical Review: ŞŞ, SK, NÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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