Early depressive manifestations in patients with dementia caused by Alzheimer's disease

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Abstract. Previous studies on the complex interplay between depression and dementia in patients with Alzheimer's disease revealed that early-life depression is a risk factor for dementia. Both depression and dementia appear to share common etiopathological mechanisms. In the present study, a comprehensive retrospective analysis was performed on a study group of patients with dementia suffering from previously diagnosed depression. The aim was to assess potentially relevant clinical and imaging parameters that can be used to characterize depression as a risk factor for dementia in later life. Statistically significant data correlating cognitive scores with the moment of depression onset and the length of time period to the diagnosis of dementia were identified. Furthermore, at the moment of depression diagnosis, structural cerebral alterations tended to appear more frequently in women compared with men. However, this sex-associated difference is not maintained after the moment of dementia diagnosis. Results from the present study contributed additional data to the evidence supporting a relationship between a history of depression and the occurrence of Alzheimer's disease, discussing relevant clinical and imaging parameters featured in patients with dementia and their inter-relations.

Introduction

As the proportion of the population aged ≥65 years is globally rapidly increasing, the number of patients with dementia is expected to double within the next 20 years (1-4). With this aging global population, a number of studies have predicted an upcoming dementia epidemic, based on the frequently observed notion that cognitive decline is associated with advancing age (3-5). Dementia is one of the most incapacitating diseases in elderly patients, representing 1/6 of all disability adjusted life years in older individuals (4,5). Alzheimer's disease (AD) is the most prevalent type of dementia, accounting for 60-70% of the ~55 million individuals with dementia worldwide (1-4). Therefore, early detection of dementia would allow the prompt implementation of measures that can potentially delay the cognitive impairment or even prevent the associated neurodegeneration.

Cognitive impairment and dementia are widely considered to be the biggest contributors to the drain of resources associated with patient care compared with that incurred by other chronic diseases (such as cardiovascular) and impairments (6). The associated burden of care has been previously found to be related to the severity of dementia. The cognitive and functional decline this disease causes, negatively affects the patient's ability to be independent and to engage in daily activities. The rising prevalence rates of dementia due to population aging and growth, in addition to the absence of curative therapies, cast a somber picture for the future of patients with dementia (3).

Depression has been increasingly reported as being one of the leading causes of psychiatric and medical morbidity and mortality amongst the elderly population. It is estimated that 10-15% of the AD cases may be attributed to depression, whereas 25% reduction in the prevalence rate of depression may result in the decrease in global cases of AD by 827,000 (7). In addition, available data are suggesting that depression occurs in 20-30% patients with AD, though this proportion is likely to be even higher in patients diagnosed with vascular dementia or Lewy body dementia (8). In particular, late-life depression has been associated with a 2X increase in the risk of developing different types of dementia (9). The majority of previous studies that focused on the relationship between depression and dementia, especially that caused by AD, reported that there is a positive association between the two entities. There is accumulating evidence supporting both hypotheses that early life depression is a risk factor for dementia in later life and later-life depression is a prodrome to dementia (1).

Age of onset of the first depressive episode has been reported to be associated highly with depression length and burden, meaning that it may be applied as a useful marker for phenotypic distinction. The etiopathogenicity of depression

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is multifactorial, with various factors observed to influence both the severity and age of debut. Early-onset depression is considered to be associated with family history and genetic predisposition, whilst late-life depression appears to be more associated with the vascular burden and other pathological degenerative processes. Patients suffering from depression early in life may experience cognitive impairment due to lengthier depressive episodes, leading to hippocampal atrophy, increased allostatic load and reduced brain reserve (10,11). In addition, several studies have revealed that patients with late-life depression exhibited more significant cognitive impairment at baseline followed by significant subsequent decline, whilst patients with early-onset depression tended to suffer from substantial impairment later, followed by an important consecutive decline (11-13).

There is also substantiation from previous clinical studies demonstrating that both conditions exhibit similar neurobiological changes, such as white matter disease, suggesting either shared risk factors or shared pattern of neuronal damage. Various biomarkers that can be assessed by neuroimaging or laboratory testing of biological samples, such as functional impairment, neuronal loss and protein deposition, were previously compared. Several neuropathological abnormalities were found to be commonly associated with depression, including amyloid depositions, cerebral or hippocampal atrophy, reduced volume in the basal ganglia and prefrontal regions and high levels cerebrovascular injury-inducing inflammatory plasma markers and glucocorticoids (13,14). These findings suggest similarities between the two clinical entities, although different cognitive stages or manifestations may be present among patients with depression with similar biomarker profiles (2,15). However, the current clinical assessment methods lack measurements for daily clinical practice that can be used to identify the early risk of dementia in patients manifesting unspecific symptoms. The present study aimed at validating the hypothesis of the link between early depression and consecutive dementia, providing an in-depth analisys of the correlations between relevant clinical parameters measured comparatively at baseline when depression was diagnosed and later in life when dementia was diagnosed.

Materials and methods

The present study is a retrospective study designed to analyze the relevant demographic and clinical parameters of depression in a study group of 103 patients aged >60 years (35 men and 78 women, mean age -74.77 years with standard deviation 7.305) who were hospitalized within a period of 9 years (January 2013-December 2021) in two centers, namely 'Elisabeta Doamna' Psychiatric Hospital of Galati (Galati, Romania) and in the Geriatric Clinic 'St. Apostle Andrei' Clinical Emergency County Hospital in Galati (Galati, Romania). These patients were diagnosed with AD during the follow-up period, using the definitions of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (1,12). Inclusion criteria referred to: age >60 years old, patients previously diagnosed with depression, and valid cognitive assessment performed both at depression onset and at the moment AD was diagnosed. Exclusion criteria contained age <60 years old, lack of complete cognitive assessment or lack of patient consent for research use of data.

In total, the following two main milestones were defined: The baseline was set as the onset of the depressive disorder, whereas the comparison threshold was the moment of AD diagnosis. The assessment was performed by the hospital geriatrician, psychiatrist and psychologist based on the standard clinical protocols (like the Geriatric Comprehensive Assessment).

In the study group, cognitive function was assessed using the following basic standard clinical tools: Mini Mental State Evaluation (MMSE); Clock Drawing Test and Montreal Cognitive Assessment (16-18). The MMSE score values were used as a basis for the statistical analysis.

The majority of patients (54.2%) included in the present cohort study were evaluated using widely available cerebral imaging techniques, namely native computed tomography (CT)-scanning and/or magnetic resonance imaging (MRI), with all available imaging data retrospectively analyzed.

Software used for statistical analysis was SPSS Statistics 23 (IBM Corp.). Statistical analyses, such as independent samples test-t-test for Equality of Means/Levene's test for equality of variances, descriptive statistics for group evaluation and the ANOVA method.

For ordinal values the Spearman correlation coefficient (ρ) was calculated, in addition to the associated probability, using the significance threshold α=0.05. A correlation between the variables would be considered if P<0.05 was found between the variables, whereas the P-value provides the correlation degree, which range between +1 and -1. The correlation level closer to +1 or -1 reflects a higher degree of correlation in direct proportion for positive values (+) or inversed for negative values (-), respectively. To check if the values are normally distributed, the Kolmogorov Smirnov test was utilized. The values of φ, C, V correlation coefficients were calculated for the nominal data analysis in addition to their associated probabilities. A χ^2 test on these data was applied to see if there is an association between variables.

Paired T-test for two independent samples was used to test for statistically significant differences between mean values of the same variable (cognitive function defined by the MMSE score at the two set thresholds, namely the baseline of the depression onset and the moment of AD diagnosis) in 2 subgroups defined by sex (male and female), living background of patients (rural/urban) or the manifestation of a certain symptom (defining the subgroups of patients showing that particular symptom or not). The equality of the variances was tested using the Levene's test, with a statistical significance threshold at P<0.05.

The present retrospective analysis and subsequent study publication was approved by the Hospital Ethics Committee 'Elisabeta Doamna' Psychiatric Hospital of Galati, (approval no. 4/11.03.2019); Hospital Ethics Committee of the 'St. Apostle Andrei' Clinical Emergency County Hospital in Galati, (approval no. 29955/25.11.2022) and was conducted according to the Declaration of Helsinki (19). No Artificial Intelligence (AI) software was used for data collection, statistical analysis or the preparation of the manuscript.

Results

Baseline characteristics. The study group included 103 patients diagnosed with AD, with 35 (34%) men and 68 (66%) women and 59 (57.3%) of which living in urban areas.

The median age of the entire study group was 74.7 years old (60-89 years old range). From the perspective of depressive symptoms onset, for the majority of patients this took place <5 years before their AD diagnosis (75 cases, 72.8% of the study sample; Fig. 1). These patients were frequently admitted to hospital multiple times in between the date of first depression onset and AD diagnosis, 50.5% of whom being hospitalized ≥5 times for various psycho-neurocognitive complaints. Specifically, the average number of hospitalizations in the trial cohort was 6.5 (standard deviation -4.8), with a total of 1,168 days of hospital stay (average, 11.3 days; range, 1-44 days, standard deviation -59.854). Regarding the deterioration of cognitive deficiency in the present cohort study, the mean MMSE scores varied from 25.39±1.981 at the moment of depressive disorder diagnosis (range, 21-30) to 16.76±3.142 when dementia was diagnosed (range, 8-22). The Kolmogorov Smirnov confirmed that the MMSE scores follow a normal distribution.

Correlations identified between set parameters. A strong correlation was identified between the duration (years) from the onset of depression to dementia diagnosis and the value of the MMSE score at the moment of depression diagnosis (ρ=0.534; P<0.01; Fig. 2A). The onset of the first depressive episode was found to correlate with the year of dementia diagnosis (ρ=0.362; P<0.01; Fig. 2B), suggesting an earlier onset of dementia if the depression onset was also earlier.

The onset of the first depressive episode was correlated with the MMSE score at the moment of depressive diagnosis (ρ=-0.376; P<0.01; Fig. 2C). Because this correlation index has a negative value, this indicates an inversed proportionality between the two variables. This suggests that a lower MMSE score is correlated with an earlier onset of depression, therefore a more important cognitive deficit.

The MMSE score at the moment of depression diagnosis was found to be directly correlated with the total number of days of hospitalization (ρ=0.307; P=0.02; Fig. 2D) and the number of hospitalizations between depression onset and dementia diagnosis (ρ=0.303; P=0.02; Fig. 2E), but not with the duration of hospitalization at the first admittance into a healthcare service (ρ=-0.069; P=0.489; Fig. 2F).

Analyzing the relationship between age and cognitive function, no correlation could be found between these two parameters. Age is not correlated with either the MMSE score at the moment of depression diagnosis (ρ=0.066; P=0.507; data not shown) or dementia (ρ=-0.159; P=0.109; data not shown). This suggests that although cognitive decline is possibly associated with age, the impact of age is limited in determining the evolution of cognition between first depressive symptoms and the actual diagnosis of dementia.

Symptoms associated to the onset of the depression, analyzed by sex. Anhedonia and depressive mood were presented by all study subjects, irrespective of sex. A difference was found with regards to the tendency to frequent crying spells and tearfulness, manifesting in ~50% of the study cohort but with different incidences between men and women (20% of men and 66% of women). With P<0.001, an association was found between crying and sex (χ^2=19.710; φ=0.437; Cramer's V=0.431; Contingency coefficient=0.401; Table I).

Table I. Correlation analysis of easy crying spells by sex.

A, Crosstabulation for sex and easy crying spells

Parameters	Easy crying spells and tearfulness: No	Easy crying spells and tearfulness: Yes	Total
Sex			
Male	28	7	35
Female	23	45	68
Total	51	52	103

B, Correlation parameters for nominal variables

Parameters	Value	P-value
Pearson chi-square (χ^2)	19.710	<0.001
Phi	0.437	<0.001
Cramer's V	0.431	<0.001
Contingency coefficient	0.401	<0.001

In addition, a direct but weak association was found between sex and the loss of appetite as a depressive symptom (χ^2=13.352; φ=0.360; V=0.360; C=0.339; P-value <0.001 < α=0.05; data not shown). Specifically, 76.47% women manifested a loss of their appetite, whilst only 40.0% men presented with this symptom.

No association between sex and insomnia as a common symptom for depression (χ^2=2.046; P=0.145 and φ=0.141; V=0.141; C=0.140; P=0.15305; data not shown) or psychomotor unrest (χ^2=0.281; P=0.596 and φ=V=C=0.052; P=0.59605; data not shown) could be found.

Association analysis of cerebral imaging. A significant association of sex with cerebral abnormalities identified by native CT-scan/MRI at the moment of dementia diagnosis was found (χ^2=7.094; φ=0.262; V=0.262; C=0.254; P=0.029). In the subgroup of women with modified cerebral imaging, 25% presented cortical atrophy whereas 69.1% had both cortical and subcortical atrophy. There is a different split in the subgroup of men with cerebral imaging disturbances. Specifically, 48.5% presented with cortical atrophy, none showing only white matter abnormalities, whilst 51.4% presented both generalized cortical and subcortical atrophy (Table II).

ANOVA of the mean MMSE scores at the moment of AD diagnosis, comparing the three defined subgroups based on the type of cerebral degenerative lesions, namely clustered as cortical, subcortical and both cortical and subcortical atrophy, revealed no statistically significant difference among the three patient subgroups (P=0.066; Fig. 3).

In the present patient sample lot, analysis of cerebral atrophy was used as the main structural abnormality detected by imaging (native CT-scanning or MRI), which revealed that

Table II. Crosstabulation for sex and cerebral abnormalities identified by native CT-scan/MRI imaging at the moment of dementia diagnosis.

A, Cerebral abnormalities (native CT-scan/MRI imaging) at the moment of dementia diagnosis

Sex	Cortical atrophy	Subcortical atrophy	Both cortical and subcortical atrophy	Total
Male	17	0	18	35
Female	17	4	47	68
Total	34	4	65	103

B, Correlation parameters for nominal variables

Parameters	Value	P-value
Pearson chi-square (χ^2)	7.094	0.029
Phi	0.262	0.029
Cramer's V	0.262	0.029
Contingency coefficient	0.254	0.029

CT, computed tomography; MRI, magnetic resonance imaging.

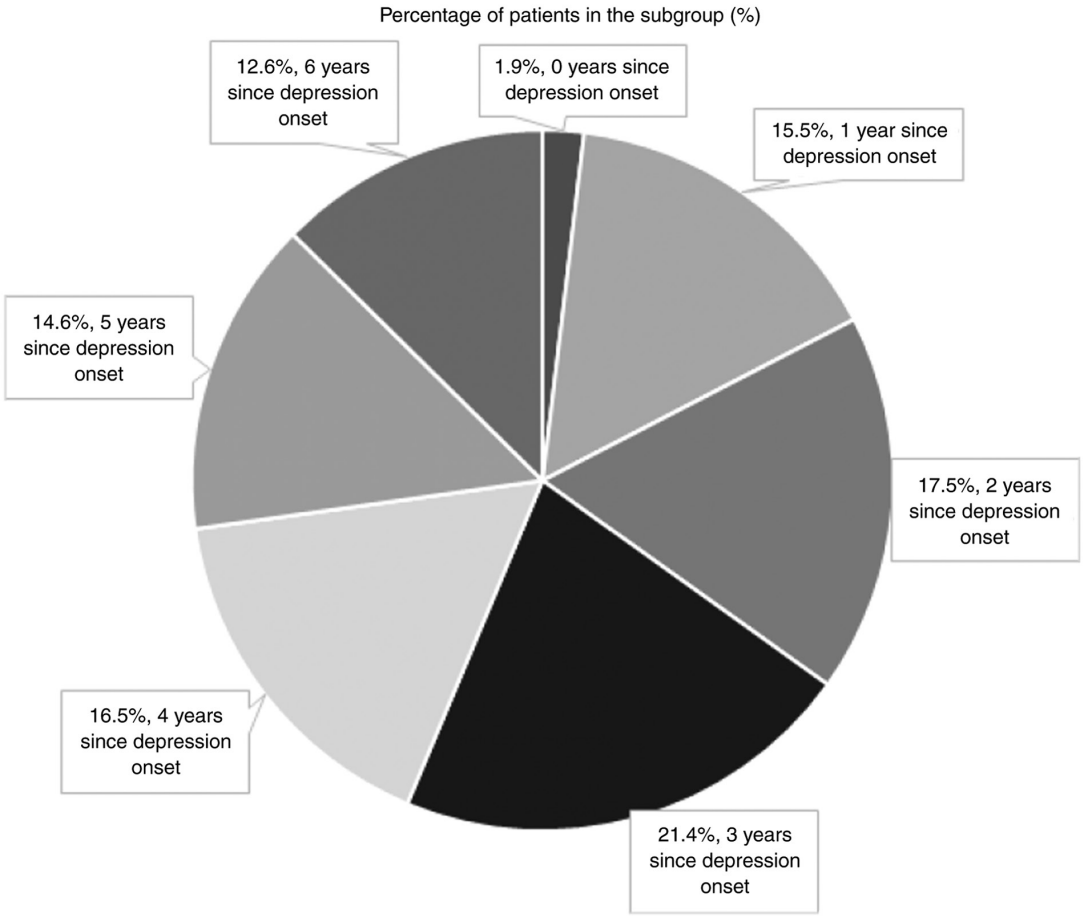

Figure 1. Time from the depression onset to dementia diagnosis in years.

the majority of patients examined at the moment of AD diagnosis were already presenting both cortical and white matter atrophy (63.1% of the patients; Fig. 4A-C).

Cognitive function analysis using t-test for two independent samples. Levene's test confirmed the equality of variances for the MMSE score values at the moment of depression

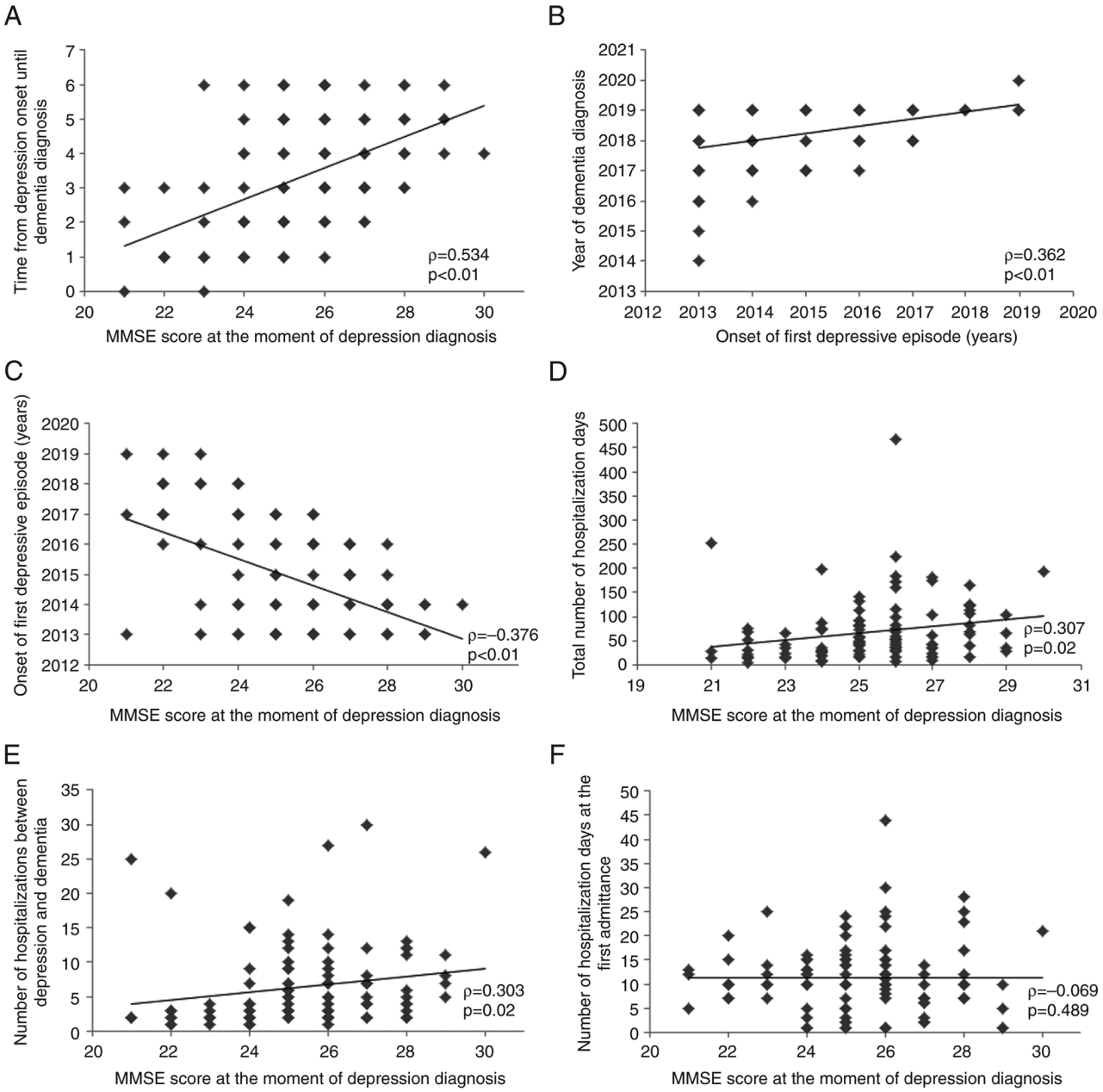

Figure 2. Graphical representation of the correlation between variables. (A) Time from depression onset until dementia diagnosis. (B) Years of dementia diagnosis. (C) Onset of first depressive episode. (D) Total number of hospitalization days. (E) Number of hospitalizations between depression and dementia. (F) Number of hospitalization days at the first admittance. MMSE, Mini Mental State Evaluation.

onset for the two groups determined by sex. Variances were not equal in the case of the MMSE scores the moment of AD diagnosis. The t-test for the MMSE score at the moment of depression onset, considering the two independent subgroups defined by sex, indicated that there was no statistically significant difference between men and women (P=0.316 > α=0.05). However, at the moment of AD diagnosis, the situation changed, with significantly higher MMSE values in the women subgroup compared with those in the men subgroup (P=0.022; Table III).

Clinical symptoms analysis using t-test for two independent samples. Regarding clinical symptoms, a comparative t-test could not be applied for anhedonia and depressive mood, as all patients presented them when the depressive disorder occurred. For crying and tearfulness, there was no statistically significant difference between patients presenting these and those who did not at the moment of depressive symptom onset regarding the MMSE scores. Incidence of insomnia at the moment of the occurrence of depression had no influence on the mean MMSE score value (P=0.254 > α=0.05; Table IV), stating the same for psychomotor unrest (P=0.459 > α=0.05; Table V).

Regarding the MMSE scores at the moment of depression occurrence were found to be higher for patients reporting maintained appetite compared with those in patients who lost appetite (P=0.032; Table VI).

Independent paired t-test between the patient subgroups with or without a certain clinical feature at the moment of AD diagnosis revealed significantly lower MMSE scores

Table III. Group statistics of cognitive status by sex (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Sex	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of depression onset	Male	35	25.11	2.069	0.350
	Female	68	25.53	1.935	0.235
MMSE score values at the moment of dementia diagnosis	Male	35	15.66	3.694	0.624
	Female	68	17.32	2.673	0.324

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of depression onset	Equal variances assumed	0.072	0.789	-1.007	0.316	-0.415	0.412	-1.233	0.403
MMSE score values at the moment of dementia diagnosis	Equal variances not assumed	7.773	0.006	-2.369	0.022	-1.666	0.704	-3.078	-0.255

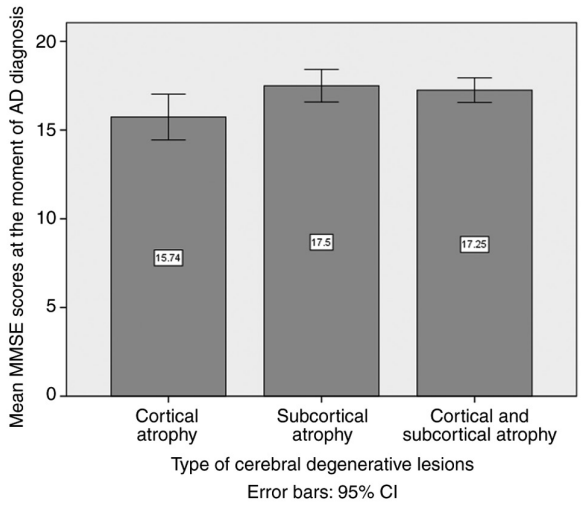

Figure 3. The mean MMSE scores at the moment of AD diagnosis, comparing the three defined subgroups based on the type of cerebral degenerative lesions. MMSE, Mini Mental State Evaluation; AD, Alzheimer's disease.

in patients presenting with aphasia (P<0.001; Table VII), agnosia (P<0.001; Table VIII), temporal-spatial disorientation (P=0.008; Table IX), apraxia (P<0.001; Table X), psychomotor agitation (P<0.001; Table XI) and hallucinations (P<0.001; Table XII).

Comorbidities analysis using t-test for two independent samples. Another characteristic assessed was comorbidities associated at the moment of AD diagnosis, yielding data consistent with the previous hypothesis of etiopathological mechanisms of AD. Whilst associations with high blood pressure were found (P<0.028 < α=0.05; data not shown), no such associations could be found with dyslipidemia (P=0.591 > α=0.05; data not shown), cardiac rhythm disorders (such as atrial fibrillation; P=0.545 > α=0.05; data not shown) or diabetes (P=0.059 > α=0.05; data not shown). From the analysis, diabetes mellitus, hypertension, cardiac rhythm disorders, anemia, dyslipidemia, anxiety were found to be the most frequently associated comorbidities with the cognitive dysfunction.

In the present study, most likely due to small sample size, there was no statistically significant differences found following group division by the presence of diabetes (P=0.059), hypercholesterolemia (P=0.591), anemia (P=0.894), appetite dysregulation (P=0.246), cardiac rhythm disorders (P=0.545), anxiety (P=0.370) and chronic alcohol abuse (P=0.384); data not shown.

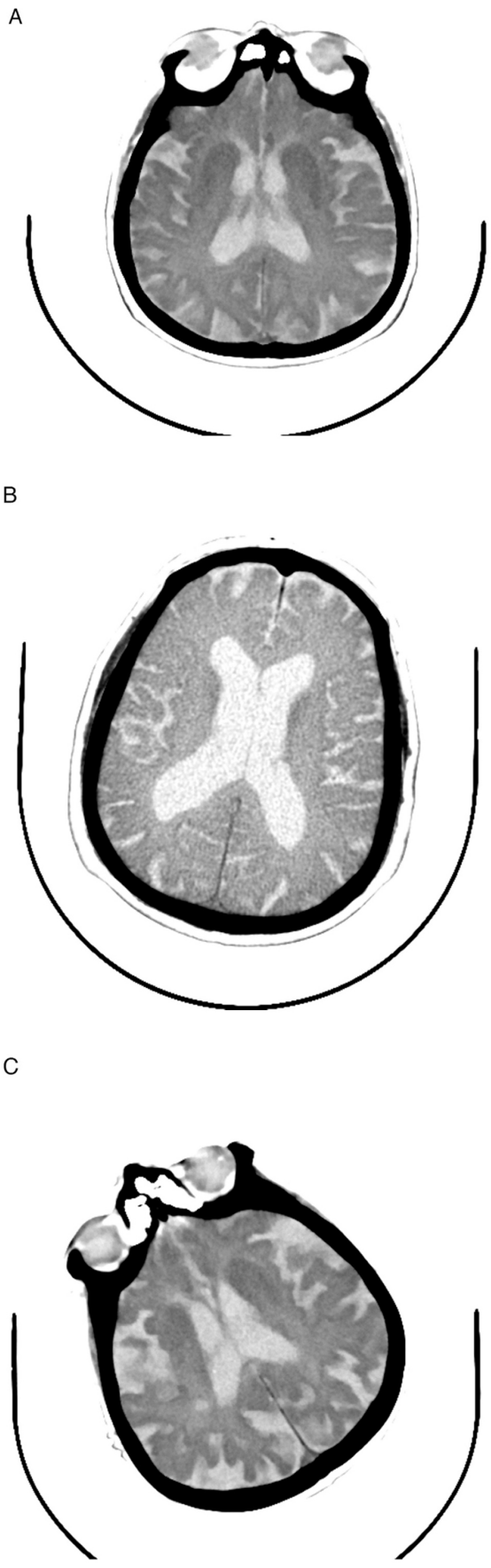

Figure 4. Cerebral CT-scanning abnormalities identified at the moment of AD diagnosis. (A) Cortical atrophy in a patient with AD. (B) Subcortical atrophy (involving the white matter). (C) CT-scan showing both cortical and subcortical atrophy in an AD patient from the study group. CT, computed tomography; AD, Alzheimer's disease.

Discussion

There is accumulating evidence on the association between depression and subsequent dementia diagnosis, suggesting an increased risk of dementia following depression. A 2020 study of the Lancet Commission on dementia (20) previously listed depression as one of the 12 modifiable risk factors that can be addressed, resulting in the prevention or delay of ≤40% of dementias.

In AD, amyloid-β plaques and neurofibrillary tangles are extensively reported substrates that can induce disruption of neural function, culminating in neuronal cell death. A relative increase in non-neuronal cell numbers, both in the cerebral cortex and subcortical white matter, can contribute to the reactive glial cell response to neuronal death (21,22). A number of previous studies have suggested that neurodegenerative diseases are caused by cortical network dysfunction instead of dysregulation in any isolated brain region. However, the isolated brain regions that are selectively damaged are likely to act as 'nodes' in the pathological brain network (21-24). This was proposed as the 'network degradation hypotheses. According to this hypothesis, the functional circuits may disconnect or weaken due to misfolded protein aggregates, resulting in small and selectively vulnerable neuron populations. Consequently, their aberrant excitability disrupts neuronal homeostasis and function, triggering a progressive degeneration of the entire functional network (21-24).

In older adults, a deficiency in energy metabolism may translate into chronic stress and depression. Stress-related decreases in brain-derived neurotrophic factor levels, in addition to other neurotrophic factors (for example, neurotrophins), can aggravate the atrophy of main limbic structures, including the hippocampus and prefrontal cortex, further impairing cognition and awareness (23,24). Several brain proinflammatory cytokines such as interleukin 1β (IL-1β) have been reported to contribute to the pathogenesis of both major depressive disorder (MDD) and AD. Specifically, these cytokines can activate the same signaling pathways, leading to neuronal damage by triggering a cascade of cellular and tissue alterations leading to various conditions, such as chronic depression, neurodegenerative diseases and other chronic immune diseases-for instance, rheumatoid arthritis (23-27).

Although there are broad genetic data available for AD, for genes such as Apolipoprotein E, MPKA and amyloid precursor protein/presenilin-I, the majority of patients typically undergo genetic testing already at the late stages of the disease, where no intervention can prevent the occurrence of the disease and the cognitive dysfunction has already become irreversible. Studies have identified co-expressed genes for AD, type 2 diabetes mellitus (T2DM) and MDD using bioinformatics analysis (27-29). A total of seven co-deregulated genes, namely structural maintenance of chromosomes 4, cell division cycle 27, hepatocyte nuclear factor 1 homeobox A, RhoD, Cut-like homeobox 1, PDZ and LIM Domain 5 and transthyretin, were considered to have a diagnostic value for AD, T2DM and MDD (27). Another genomic study previously provided evidence for a significant causal genetic effect of depression on AD using the analysis of single nucleotide polymorphism profiles (30,31).

Table IV. Group statistics of cognitive status by symptoms at the moment of depression onset; insomnia (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting insomnia	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of depression onset	No	9	26.11	1.269	0.423
	Yes	94	25.32	2.028	0.209

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of depression onset	Equal variances assumed	2.073	0.153	1.147	0.254	0.792	0.690	2.161	-0.577
	Equal variances not assumed	7.773	0.006	1.678	0.119	0.792	0.472	1.817	-0.233

AD is an insidious, age-related neurodegenerative disorder that is clinically characterized by a variety of neuropsychological alterations, such as impaired thinking ability, cognitive decline, memory loss and behavioral impairment. By contrast, depressive disorder can manifest as sadness that is severe enough or persistent enough to interfere with a person's function by reducing the affected individual's interest or pleasure in activities (also known as anhedonia). While its diagnosis is mainly clinical, depression may be triggered by hereditary, neurotransmitter profile or neuroendocrine changes or different psychosocial factors. In particular, changes in a number of neurotransmitter levels can include the abnormal regulation of cholinergic, catecholaminergic (noradrenergic or dopaminergic), glutamatergic and serotonergic (5-hydroxytryptamine) neurotransmission. Neuroendocrine dysregulation may also be a pathological factor, with particular emphasis on the following three axes: Hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid and hypothalamic-pituitary-growth hormone (32,33). A number of these pathways were added to the therapeutic arsenal that clinicians use to manage depression at the earliest possible opportunity, where proof of changing the course towards cognitive impairment exists.

The main objective of the present study was to assess if there were any correlations between different demographic or clinical parameters to characterize the associations between the time of dementia onset and depressive symptom onset. Results from the present study partially support those previous reported studies, such as the direct correlation of the level of cognitive alteration with an earlier onset of depression and the direct association between the moment of depression onset and the one of first AD manifestations (34-44). By contrast, some conclusions from the present statistical analysis were found to be contradictory to those reported by previous studies, such as those regarding association with certain comorbidities (cardiovascular or metabolic). This is likely to be due to the small sample size of the study group and limited information on the earlier medical history of the patients.

AD is associated with multiple comorbidities and bio-medical conditions. A number of which are associated with advanced age, whilst others may be triggered by various pathological condition, such as hypercholesterolemia, hypertension, T2DM, atherosclerosis, psychosis, depression, epilepsy and sleep disorders (45,46). The comorbidities affecting patients with AD can be regarded as either risk factors for AD, or conditions arising as a consequence of the pathological processes that occur during AD. Therefore, understanding the mechanism underlying AD development and the influence of comorbidities on its pathogenesis may be crucial for creating an individualized, effective and comprehensive set of interventions for patients with AD.

Drastic alterations in structural and functional neuroimaging features are one of the main biomarkers in AD.

Table V. Group statistics of cognitive status by symptoms at the moment of depression onset; psychomotor unrest (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting psychomotor unrest	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of depression onset	No	29	25.62	1.522	0.283
	Yes	74	25.30	2.137	0.248

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of depression onset	Equal variances assumed	3.658	0.059	0.743	0.459	0.323	0.435	1.186	-0.540
	Equal variances not assumed			0.860	0.393	0.323	0.376	1.074	-0.427

Table VI. Group statistics of cognitive status by symptoms at the moment of depression onset; loss of appetite (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting loss of appetite	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of depression onset	No	37	25.95	1.632	0.268
	Yes	66	25.08	2.100	0.258

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of depression onset	Equal variances assumed	2.409	0.124	2.177	0.032	0.870	0.400	1.663	0.077
	Equal variances not assumed			2.336	0.022	0.870	0.373	1.610	0.130

Table VII. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis; aphasia (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting aphasia	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	9	19.44	1.424	0.475
	Yes	94	16.50	3.144	0.324

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of dementia diagnosis	Equal variances assumed	5.697	0.019	2.772	0.007	2.944	1.062	5.051	0.838
	Equal variances not assumed			5.122	<0.001	2.944	0.575	4.158	1.731

Table VIII. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis; agnosia (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting agnosia	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	40	18.60	2.098	0.332
	Yes	63	15.59	3.145	0.396

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of depression onset	Equal variances assumed	10.394	0.002	5.346	<0.001	3.013	0.564	4.131	1.895
	Equal variances not assumed			5.830	<0.001	3.013	0.517	4.038	1.988

Table IX. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis; temporal-spatial disorientation (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting temporal-spatial disorientation	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	20	18.15	2.277	0.509
	Yes	83	16.42	3.239	0.356

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of dementia diagnosis	Equal variances assumed	6.432	0.013	2.252	0.026	1.728	0.767	3.251	0.206
	Equal variances not assumed			2.783	0.008	1.728	0.621	2.984	0.473

AD neuroimaging initiative (ADNI) is a currently ongoing, naturalistic study designed to understand the structural, biochemical and cognitive changes that occur during AD progression (47). ADNI provides evidence of increased brain atrophy in several frontal brain areas. In addition, there is available data suggesting a direct association between the neuropsychiatric symptoms manifested by patients with AD and brain morphology changes, mainly atrophy of the fronto-temporal brain structures (48-53).

The complex relationship linking dementia and depression has several underlying neuropathological mechanisms, such as increased hippocampal alterations and tangle formation in patients with AD and a history of depression (49-53). In addition, decreased cortical thickness, white matter loss and alterations in the hippocampal region were associated with both depressive symptoms and impairment of cognitive functions (49-53).

Regardless of the age at onset, patients with AD will typically require lifelong treatment. Therefore, early diagnosis and treatment will likely improve their long-term prognosis and quality of life. Exploring how interventions can effect the modifiable risk factors and how efficiently novel biomarkers can be exploited to provide objective evidence for early diagnosis, are in urgent demand. Furthermore, identification of sensitive and specific novel biomarkers, in addition to actionable and modifiable risk factors is currently a topic of intense research. Effective dementia biomarkers aid in the early identification and differential diagnosis, whilst also contribute an essential step towards developing personalized approaches and new drug therapies.

The present study has certain limitations that should be considered when interpreting the results, especially when validating previously accepted hypotheses regarding comorbidities. The relatively small sample size, the type of the present study-namely retrospective- and the lack of longitudinality, should be considered. In addition, all patient cases were analyzed only at the level of one academic center although the cases were gathered from two hospitals. Nevertheless, a comprehensive set of clinical characteristics was used to compare the two relevant thresholds in the pathogenic progress of depression towards dementia to thoroughly characterize the suggestive clinical features. The analysis was performed on widely available, brief standard examinations, where measures were taken to ensure the generalizability of results from the perspective of patient lot heterogenity. Therefore, the findings of the present study should be suitable for clinicians in any type of clinic and not only research centers.

Despite the wealth of research evidence over the past two decades, the relationship between AD and depression remains completely understood, where a highly complex interplay involving multifactorial and diverse influences likely exists. If aging, AD and depressive disorders share a common biological basis in pathophysiology, any common therapeutic

Table X. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis; apraxia (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting apraxia	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	53	17.94	2.735	0.376
	Yes	50	15.50	3.079	0.435

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of dementia diagnosis	Equal variances assumed	2.539	0.114	4.264	<0.001	2.443	0.573	3.580	1.307
	Equal variances not assumed			4.294	<0.001	2.443	0.575	3.585	1.302

Table XI. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis-psychomotor agitation (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting psychomotor agitation	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	47	17.89	2.513	0.367
	Yes	56	15.80	3.316	0.443

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of dementia diagnosis	Equal variances assumed	7.365	0.008	3.549	0.001	2.090	0.589	3.258	0.922
	Equal variances not assumed			3.634	<0.001	2.090	0.575	3.231	0.949

Table XII. Group statistics of cognitive status by symptoms at the moment of dementia diagnosis; hallucinations (unpaired t-test for equal variance; Welch's t-test for unequal variance).

A, Descriptive statistics

Parameters	Manifesting hallucinations	N	Mean	Std. deviation	Std. error mean
MMSE score values at the moment of dementia diagnosis	No	62	17.63	2.638	0.335
	Yes	40	15.30	3.330	0.526

B, Independent samples t-test data analysis

		Levene's test for equality of variances		T-test for equality of means					
								95% confidence interval of the difference	
Parameters		F	P-value	t	P-value	Mean difference	Std. error difference	Upper	Lower
MMSE score values at the moment of dementia diagnosis	Equal variances assumed	4.254	0.042	3.923	<0.001	2.329	0.594	3.507	1.151
	Equal variances not assumed			3.732	<0.001	2.329	0.624	3.574	1.084

tools could- and should-be investigated for their effects on prevention and treatment.

To concude, the results of the present comprehensive analysis on the association between AD dementia and early-manifesting depression in geriatrically hospitalized patients support the idea of standardizing a clinical assessment protocol for evaluating the cognitive dysfunction in all patients with depression and monitoring their progress as they age. Since effective treatment methods for AD dementia remain scarce, patients would benefit from the clinicians' preventive approach using the identification of high-risk individuals and potentially modifiable risk factors, namely depression.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FS and VDO conceived the study. ML and AR developed methodology and validated the data. VDO conducted formal analysis and project administration, performed data visualization and wrote the original draft of the manuscript. FS performed data curation and conducted investigation. AR and ML wrote, reviewed and edited the manuscript. ML supervised the study. AR acquired funding. All authors have discussed the results and read and approved the final version of the manuscript. FS, VDO and AR confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and was approved (approval no. 4/11.03.2019) as doctoral research by 'Elisabeta Doamna' Psychiatric Hospital Ethics Committee (Galati, Romania) and additionally also approved by (approval no. 29955/25.11.2022) Hospital Ethics Committee of the 'St. Apostle Andrei' Clinical Emergency County Hospital (Galati, Romania). Due to the retrospective nature of this study, individual patient consent for use of their data was not necessary and was waived by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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