



## Research Article

# Nutritional Status of Alzheimer's Patients in a Geriatric Clinic in Dakar: A 10-Month Prospective Descriptive Study

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## Abstract

**Background:** Malnutrition refers to a state of nutritional imbalance in the body. It is characterized by a negative energy and/or protein balance. Malnutrition is common in patients with dementia, particularly Alzheimer's disease. Epidemiological data show that weight loss appears to increase as the disease progresses. It is thought to be a predictor of mortality in patients with Alzheimer's disease because it is accompanied by severe events. The study of malnutrition in patients with Alzheimer's disease appears to be essential. Few studies have focused on the relationship between nutritional status and cognitive status. In Senegal, only one study has looked at Alzheimer's disease (AD) in the elderly, and the nutritional status of patients was not specifically assessed. We therefore decided to conduct this pioneering study in the geriatric population with AD in Senegal, with the primary objective of describing the epidemiological, clinical, paraclinical, and therapeutic aspects of malnutrition in our patients with AD in the geriatrics and gerontology department of the Fann National University Hospital Center in Dakar. **Methods:** This was a prospective, descriptive study conducted over a 10-month period from December 2022 to October 2023, involving patients aged 60 and over who were seen for an initial consultation in the geriatric department of the FANN University Hospital Center. Cognitive assessment was performed using the Senegal test, and malnutrition was screened for in these patients using the MNA. Epidemiological, clinical, paraclinical, and therapeutic characteristics were collected and analyzed using epi.info.7 software. **Results:** Of the 695 patients seen during this period, thirty-two (32) had Alzheimer's disease, representing a prevalence of 4.6%. The average age of our patients was 77 $\pm$ 08 years (ranging from 6 to 92 years). The 75-79 age group (31.25%) was the most representative, followed by the 70-74 age group (21.88%). There was a predominance of women (68.75%), with a male/female ratio of 0.45. The main comorbidities were high blood pressure (62.65%) and diabetes (34.38%). The history of the disease was dominated by falls (15.63%). The main reason for consultation was memory disorders (100%). The duration of the disease was between 6 months and 1 year in 40.6% of patients. The Senegal test was the diagnostic tool used to screen for Alzheimer's disease. Cognitive impairment according to the Senegal test appeared severe in 7 patients (21.87%), moderate in 4 patients (12.5%), and mild in 21 patients (65.63%). Geriatric syndromes were dominated by frailty (56.25%) and loss of functional independence (43.75%). Twelve patients (37.5%) were malnourished (MNA score below 17), 17 patients (53.12%) were at risk of malnutrition (MNA score between 17 and 23.5), and three patients were not malnourished (MNA score greater than or equal to 24). None of our patients were able to undergo testing for tau, phosphorylated tau, and  $\beta$ -amyloid proteins. The most common biological abnormalities were anemia (89.28%), followed by hypoalbuminemia (81.28%). Brain MRI performed on all our patients revealed hippocampal atrophy. The severity of the atrophy was specified in only 19 patients. The atrophy was grade 2 in 9 patients (28.13%), grade 3 in 3 patients (9.37%), grade 4 in 7 patients (21.87%), and unspecified in 13 patients (40.62%). Anticholinesterase inhibitors were the drug treatment of choice in our series, with 62.62% of patients receiving them. 37.38% received memantine. **Conclusion:** AD almost always progresses to malnutrition. It is important to screen for malnutrition systematically and early in order to develop care plans.

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**Received:** 3 September 2025; **Accepted:** 3 November 2025; **Published:** 27 February 2026



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## Keywords

Elderly Subject, Alzheimer's Disease, Malnutrition, Geriatric, Fann, Senegal

## 1. Introduction

Malnutrition refers to a state of nutritional imbalance in the body. It is characterized by a negative energy and/or protein balance. It may be linked to one or a combination of the following factors: A protein-energy deficiency, An increase in total energy expenditure, An increase in energy and/or protein losses [1]. A study conducted in Senegal by Coume et al in 2014 found a high prevalence of malnutrition among hospitalized elderly patients, ranging from 30% to 70% [2]. In a report, the French High Authority for Health states that 4% of elderly people living at home suffer from malnutrition. For elderly people in institutions, it is estimated that a quarter of them are malnourished, and during hospitalization, the rate of malnutrition can reach 60% [3]. Malnutrition is common in patients with dementia, particularly Alzheimer's disease [4]. Epidemiological data show that weight loss appears to increase as the disease progresses. From the onset of the illness, patients experience difficulties in eating properly, especially as cognitive disorders worsen. It is thought to be a predictor of mortality in patients with Alzheimer's disease [5] because it is accompanied by severe events [6]: repeated infections due to impaired immune function, iatrogenic medication, worsening of existing cognitive and behavioral disorders, falls, sarcopenia, osteopenia, bedsores, fractures, or bedriddenness. These complications are associated with significant morbidity, loss of quality of life (loss of independence and dependence), and suffering for patients and families, with a significant psychosocial and economic burden. The factors leading to malnutrition in Alzheimer's disease are numerous and complex. Numerous studies confirm the clinical observation that malnutrition frequently occurs in patients with Alzheimer's dementia [7]. Berlinger et al. [8] reported close correlations between weight loss, disease duration, and cognitive status. Guyonnet et al. [6] followed 76 subjects (mean age 75 years), living at home and presenting with mild to moderate Alzheimer's disease, for one year. They had observed malnutrition in most patients with dementia. They also identified the family burden, measured by the Zarit scale, as being associated with weight loss, with the family appearing unable to manage care. According to some authors [9], malnutrition results from the onset of physical or iatrogenic disabilities and behavioral disorders related to the disease, leading to decreased caloric intake: mood problems, increasing dependence on activities of daily living. According to other studies [10], the disease is accompanied by an increase in energy requirements. Behavioral disorders such as agitation and wandering would increase caloric needs and

could be responsible for malnutrition despite the apparent consumption of sufficient amounts of food [6]. At more severe stages, refusal to eat may manifest through oppositional attitudes and defensive reflexes. Disorders of an apraxic nature can also complicate food intake. In a study conducted in France, a prevalence of malnutrition of 4.6% was found among patients with AD [11]. Another study conducted by Soysal found a prevalence of 25% among patients with AD [12]. The study of malnutrition in patients with Alzheimer's disease appears to be essential. It provides a better understanding of the natural history of the disease to predict when unexplained weight loss is a cause or a consequence of the neurological changes associated with the disease. In Senegal, only one study has looked at AD in the elderly, and the nutritional status of patients was not specifically assessed [13]. We therefore decided to conduct this pioneering study in the geriatric population with AD in Senegal, with the primary objective of describing the epidemiological, clinical, paraclinical, and therapeutic aspects of malnutrition in our patients with AD.

## 2. Materials and Methods

This was a prospective, descriptive study conducted over a 10-month period from December 2022 to October 2023, involving patients aged 60 years and older who were seen in consultation at the geriatric department of the FANN University Hospital Center. Patients with AD based on the NINCDS-ARDA criteria revised by Dubois et al [14] were included. All patients with major neurocognitive disorders other than AD and who did not meet our criteria were excluded. Malnutrition was screened for in these patients using the MNA [15]. The parameters studied were:

-*Socio-demographic data*: age, gender, level of education, previous occupation, religion, marital status, family situation (living alone or with family), care

-*Medical and surgical history, and comorbidities*: Multimorbidity was defined as the presence of at least four conditions and polypharmacy as the use of at least five medications per day.

-*Diagnostic data*

Due to the difficulty of performing biomarker assays because of their high cost, the unavailability of PET scans, and the difficulty of carrying out genetic tests in our regions, we diagnosed Alzheimer's disease (AD) based on the NINCDS-ARDA criteria revised by Dubois et al [14], which seemed

more appropriate to us. These criteria notably rely on major criterion A, which is primarily clinical, and on secondary criterion B (atrophy of the internal temporal structures such as the hippocampus, entorhinal cortex, or amygdal).

*Cognitive assessment:* neurocognitive disorders were objectively assessed on the basis of a screening with the Senegalese neurocognitive test for a score below 28/39 [16].

*Duration and severity of neurocognitive disorders.* We considered neurocognitive disorders to be mild for scores between 16 and 28, moderate for scores between 9 and 16, and severe for scores between 0 and 9.

*Evidence of encoding disorders specific to Alzheimer's disease* with a memory deficit not significantly improved by cueing. Items concerning immediate and delayed recall in the Senegal test were studied. We considered any item for immediate and delayed recall with a score below 50% of the maximum value to be abnormal.

*Psycho-behavioral disorders* by looking for various disorders that could be found in Alzheimer's disease (psychomotor agitation, hallucinations, insomnia, delusions, anxiety, euphoria, disinhibition, apathy, refusal to eat, irritability).

#### *Standardized geriatric assessment*

Patients underwent a multidimensional geriatric assessment using internationally validated scales: Senegal test for neurocognitive disorders, Geriatric Depression Scale (GDS) for screening for depression, Katz Activities of Daily Living (ADL) for functional autonomy, Fried score for frailty, and Mini-Nutritional Assessment (MNA) for nutritional status.

#### *- Paraclinical data*

*Biology:* Hemoglobin level, CRP (C-reactive protein), serum albumin, corrected calcium, sodium, potassium, urea, creatinine, vitamin D.

*- Magnetic resonance imaging (MRI):* Search for hippocampal atrophy with severity according to the Scheltens classification [17].

#### *Operational definitions of variables*

- We considered the following:

Any patient with an MNA score below 17 as malnourished and any patient with an MNA score below 17 and hypoalbuminemia below 30g/l as severely malnourished.

At risk of malnutrition: any patient with an MNA score between 17 and 23.5.

A normal nutritional status for any patient with an MNA score greater than or equal to 24.

Regarding biology:

Anemia: hemoglobin level < 12g/dl in women and 13g/dl in men

Positive CRP: CRP level > 6mg/l;

Hypoalbuminemia: serum albumin level < 35 g/L Hypocalcemia: calcium level < 81 mg/L

Hypercalcemia: Calcemia > 104 mg/L

Hyponatremia: natremia < 135 mEq/L

Hypernatremia: natremia >145 mEq/L

Hypokalemia: potassium level < 3.5 mEq/L

Hyperkalemia: Potassium level > 5.3 mEq/L (taken without tourniquet)

Elevated creatinine if >115 µmol/L

Renal failure: Glomerular filtration rate (GFR) less than 90 ml/min/1.73 m<sup>2</sup>.

Severity was subdivided into 5 stages:

Stage 1: Normal GFR greater than 90 ml/min/1.73m<sup>2</sup>

Stage 2: Mild renal impairment GFR between 60 and 89 ml/min/1.73m<sup>2</sup>

Stage 3: Moderate CKD GFR between 30 and 59 mL/min/1.73 m<sup>2</sup>

Stage 4: Severe CKD, GFR between 15 and 29 ml/min/1.73m<sup>2</sup>

Stage 5: End-stage CKD GFR less than 15 mL/min/1.73 m<sup>2</sup>

#### *Data entry and Analysis*

A form was designed to collect data on the study variables. We completed it using Epi Info 7. The data were collected on a pre-established data collection form. They were entered and analyzed using Epi.info version 7 for Windows software. The descriptive study was carried out by calculating frequencies for qualitative variables and calculating means and standard deviations for quantitative variables.

#### *Ethical considerations*

For our study, ethical approval was not required according to Senegalese national regulations. At most, the free consent of the patient or legal guardian was obtained, and authorization was granted by the head of the department. Access to the data is limited to the study team, and the confidentiality of the information has been ensured.

## 3. Results

### 3.1. Epidemiological Characteristics

During the study period, 695 patients were seen in consultation at the department. Of these patients, 51 presented with major neurocognitive disorders, representing a prevalence of 7.33%. Of these 51 patients, 32 had Alzheimer's disease, representing a hospital prevalence of 4.6%. Among Alzheimer's patients, 12 were malnourished, representing a prevalence of 37.5%.

The average age of our patients was 77+/-08 years, ranging from 60 to 92 years. The 75-79 age group (31.25%) was the most representative, followed by the 70-74 age group (21.88%). There was a predominance of women (68.75%), with a male-to-female ratio of 0.45. Nineteen patients (59.38%) lived without a spouse (widowed) and 40.63% were married. Almost all of our patients lived with their families (96.88%). In 43.75% of cases, they had no formal education. None of the patients were currently employed. The main medical history and comorbidities were hypertension (62.65%), diabetes (34.38%), and falls (15.63%) (Table 1). A family history of dementia was found in 17.25% of cases.

**Table 1.** Sociodemographic characteristics/history of comorbidities.

| Variables studied                      |                   | Number (N=32) | Percentage |
|----------------------------------------|-------------------|---------------|------------|
| Age groups (Average age=77 years +/-8) | 60-64             | 01            | 3,12       |
|                                        | 65-69             | 04            | 12,50      |
|                                        | 70-74             | 07            | 21,87      |
|                                        | 75-79             | 10            | 31,25      |
|                                        | 80-84             | 03            | 9,38       |
|                                        | 85-89             | 05            | 15,63      |
|                                        | 90-94             | 02            | 6,25       |
|                                        | Widower (W)       | 19            | 59.38      |
| Marital status                         | Married           | 13            | 40.62      |
| Support                                | Your loved ones   | 30            | 93.75      |
|                                        | Yourself          | 02            | 6.25       |
|                                        | Insurance         | 00            | 00         |
|                                        | Not supported     | 00            | 00         |
| Geographical origin                    | Dakar Department  | 22            | 68.75      |
|                                        | Other regions     | 05            | 15.62      |
|                                        | Guediawaye        | 02            | 6.24       |
|                                        | Pikine            | 01            | 3.13       |
|                                        | Rufisque          | 01            | 3.13       |
|                                        | Sub-regions       | 01            | 3.13       |
| Current professional activity Current  | None              | 32            | 100        |
|                                        | With              | 00            | 0          |
| Religion                               | Islam             | 27            | 84.38      |
|                                        | Christianity      | 05            | 15.62      |
|                                        | Wolof             | 11            | 34.38      |
|                                        | Toucouleur        | 10            | 31.25      |
| Ethnicity                              | Serer             | 05            | 15.62      |
|                                        | Other             | 05            | 15.62      |
|                                        | Diola             | 01            | 3.13       |
|                                        | No schooling      | 13            | 40.63      |
| Level of education                     | Koranic school    | 07            | 21.87      |
|                                        | Secondary         | 06            | 18.75      |
|                                        | Higher            | 06            | 18.75      |
| Family situation                       | Lives with family | 31            | 96.87      |
|                                        | Lives alone       | 01            | 3.13       |
| Lifestyle                              | Stimulants        |               |            |
|                                        | (Tea or coffee)   | 11            | 34.38      |
|                                        | Drugs             | 00            | 00         |

| Variables studied | Number (N=32) | Percentage |
|-------------------|---------------|------------|
| Tobacco           | 00            | 00         |
| Alcohol           | 00            | 00         |

### 3.2. Diagnostic Characteristics

The main reason for consultation was memory impairment (100%). The average score on the Senegal test was 18.6, ranging from 2 to 28. Cognitive impairment according to the Senegal test appeared severe in 3 patients (10.71%), moderate in 4 (14.28%), and mild in 21 (75.01%). The duration of the disease was 6 to 12 months in 13 patients (40.62%), 2 to 3 years in 11 patients (34.38%), 4 to 5 years in 4 patients (12.5%), and 5 years or more in 4 patients (12.5%).

Geriatric syndromes were dominated by frailty (56.25%) and loss of functional independence (56%). Depression was investigated in 22 patients, of whom 4 (18.18%) had depression (Table 2). The MNA was performed in all our patients. The average was 18+/-05 with extremes ranging from 7 to 27, and the most representative items were BMI below 22 (96.87%), the existence of neuropsychological problems (96.87%), calf circumference below 31 (65.63%), weight loss (64.78%) (Figure 1). Twelve (37.5%) patients were malnourished, and 53.12% of patients were at risk of malnutrition. Only 9.36% of patients had a normal nutritional status. Regarding the MNA, among malnourished patients, 66.67% had severe malnutrition. None of our patients were

able to have their tau, phosphorylated tau, and  $\beta$ -amyloid proteins measured. The most common biological abnormalities were anemia (89.28%), followed by hypoalbuminemia (81.28%) and hypovitaminosis D (74.14%) (Table 3). The mean albumin level was 30.6+/- 6, with extremes ranging from 18 to 45.8. Magnetic resonance imaging was systematically performed on our patients and showed hippocampal atrophy in 100% of cases. The severity of the atrophy was specified in only 19 patients. The atrophy was grade 2 in 9 patients (28.13%), grade 3 in 3 patients (9.37%), grade 4 in 7 patients (21.87%), and unspecified in 13 patients (40.62%). All our patients underwent magnetic resonance imaging. The severity of the atrophy was specified in only 19 patients. The atrophy was grade 2 in 9 patients (28.13%), grade 3 in 3 patients (9.37%), grade 4 in 7 patients (21.87%), and unspecified in 13 patients (40.62%). All our patients received anti-cholinesterase treatment with donepezil (N=21) or anti-glutamatergic treatment with memantine (N=11). Four (4) patients received melatonin-based treatment, four (4) received risperidone-based treatment, and four (4) received SSRI-based treatment. All of our malnourished patients were placed on CNO. None were placed on enteral or parenteral nutrition (oral nutritional supplement).

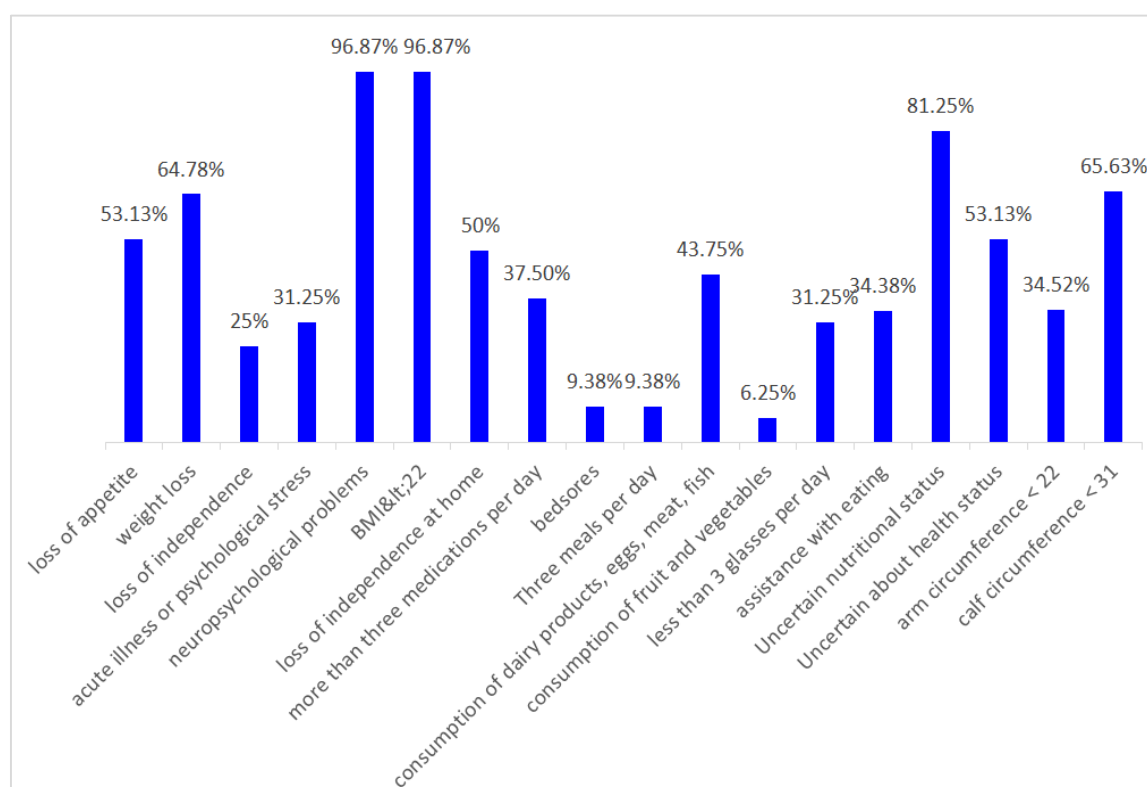
**Table 2.** Distribution according to reason for consultation, duration of symptoms, and clinical manifestations.

|                          | Modalities                      | Number (N=32) | Percentage (%) |
|--------------------------|---------------------------------|---------------|----------------|
| Reasons for consultation | Memory disorders                | 32            | 100            |
|                          | Psychomotor agitation           | 02            | 06.25          |
|                          | Insomnia                        | 01            | 03.13          |
| Duration of symptoms     | 6 months to 1 year              | 13            | 40.63          |
|                          | 2 to 3 years                    | 11            | 34.37          |
|                          | 4 to 5 years                    | 04            | 12.5           |
|                          | 5 years and over                | 04            | 12.5           |
| Psycho Psycho-behavioral | Psychomotor agitation           | 07            | 21.87          |
|                          | Insomnia                        | 11            | 34.37          |
|                          | Hallucinations                  | 02            | 06.25          |
|                          | Refusal to eat                  | 01            | 3.13           |
|                          | Logorrhea                       | 01            | 3.13           |
| Geriatric syndromes      | Frailty                         | 18            | 56.25          |
|                          | Loss of functional independence | 14            | 43.71          |

| Modalities   | Number (N=32) | Percentage (%) |
|--------------|---------------|----------------|
| Malnutrition | 12            | 37.5           |
| Depression   | 04            | 18.18          |

**Table 3.** Percentage of biological abnormalities.

| Biological abnormalities | Percentage (%) |
|--------------------------|----------------|
| Anemia                   | 89.28          |
| Hypoalbuminemia          | 81.28          |
| Hypovitaminosis D        | 74.14          |
| Impaired GFR             | 69.26          |
| Hypocalcemia             | 59.57          |
| Elevated CRP             | 23.10          |
| Hyponatremia             | 17.85          |



**Figure 1.** Representation of patient results for the various items of the MNA.

## 4. Discussion

In our study, 12 patients (37.5%) were malnourished. 17 patients (53.12%) were at risk of malnutrition and three pa-

tients were not malnourished. Although our sample is less representative, our frequency of malnutrition is higher than that reported by Broker et al [11] in their study conducted in France on the nutritional status of patients with AD. That study included 479 subjects, 22 of whom (4.6%) were mal-

nourished, while 166 patients (34.66%) were at risk of malnutrition. Ikeda et al [4] found that among elderly people with AD living in the community, 5 to 30% were malnourished, while in nursing homes, the rate ranged from 16 to 70%. In the study by P Gil Gregorio et al [18], 17.5% of Alzheimer's patients were malnourished and 68.1% were at risk of malnutrition. This prevalence could be explained by the fact that in AD, eating disorders such as refusal to eat or difficulty eating are common and lead to malnutrition [19]. In patients with dementia, cognitive impairment affects functional capacity, leading to increased dependence on others for instrumental activities of daily living, such as shopping or cooking. These activities are necessary for the patient to achieve adequate nutritional intake.

Our average MNA score was  $18 \pm 0.5$ , with extremes ranging from 7 to 27. Our average MNA score was lower than that of Ikeda et al [2], which was  $23.4 \pm 3.2$ , and that of P Gil Gregorio et al [18], which was  $20.1 \pm 3.5$  [18]. Although the MNA is no longer part of the new criteria according to the HAS, some studies find it to be more sensitive than other tools for screening for malnutrition [20].

The average age of our patients was  $77 \pm 8$  years. Our average age is similar to that reported by Brocker et al [11], which was  $77.4 \pm 7.1$  years. In a study conducted in 2020 by Soysal et al [21] on the relationship between dementia and nutritional parameters in elderly subjects, the average age of patients was  $76.87 \pm 8.15$  years. Our average age is lower than that of P Gil Grégorio et al [18], who found an average of 86.5 years. The high average age could be explained by the fact that the study was conducted in a center dedicated solely to geriatrics and by the fact that life expectancy has increased. None of our patients were alcoholics or smokers. These results could be explained by the socio-religious context, as Senegal is a predominantly Muslim country. Coffee or tea consumption was noted in 34.38% of cases. According to Ma et al [22], low coffee consumption (1 to 2 cups/day) but not high consumption ( $>3$  cups/day) was associated with an 18% reduction in the risk of AD (RR 0.82, 95% CI 0.71-0.94, compared to 1 cup/day). Certain neuroprotective components may be present in coffee or green tea consumption, such as caffeine and L-theanine. The anti-amyloid effects of green tea may protect against Alzheimer's disease, including inhibition of A $\beta$  aggregation and reduction of A $\beta$ -induced oxidative stress [22]. In the 2016 study by Miranda et al [20] of institutionalized patients with neurological disorders, malnutrition was more prevalent in patients with Alzheimer's disease, stroke, and other forms of dementia, at 100%, 87.5%, and 84.6%, respectively. Shatenstein et al. [23] followed a population of elderly Canadians for five years and noted that malnutrition was more prevalent in patients with dementia. These results show that malnutrition is a common complication of AD in the United States. This involuntary malnutrition could be the direct result of decreased food intake, which is itself a consequence of patients' loss of independence and cognitive decline.

Among our malnourished patients, 66.67% had severe malnutrition with an average serum albumin level of  $30.6 \pm 6$ , ranging from 18 to 45.8. Our results are lower than those of the Toulouse study conducted by Sylvie Lauque et al [24], which had an average serum albumin level of 38.5 g/L, ranging from 26.5 to 52. Although according to the new HAS recommendations, albuminemia is considered a criterion for the severity of malnutrition, many continue to use albuminemia as a diagnostic criterion. This is due to the lack of access to means of measuring sarcopenia. In Guillaume Ulmann's study [25], it was shown that most practitioners were unable to assess muscle mass and strength due to a lack of access to the necessary techniques, and that half of the participants used albuminemia to diagnose malnutrition. Training teams and securing funding for equipment therefore appear to be prerequisites to the successful implementation of these recommendations. In our study, 74.19% had hypovitaminosis D. This could be explained by reduced sun exposure due to either patients being confined to their homes by their families or a loss of functional independence as a result of dementia, preventing patients from being exposed to the sun.

Vitamin D deficiency is common in AD, and vitamin D may play an important role in neurogenesis. In a randomized, double-blind study, 210 patients with Alzheimer's disease received 800 IU/day of vitamin D for 12 months. They demonstrated that daily oral vitamin D supplementation (800 IU/day) for 12 months could improve cognitive function and reduce A $\beta$ -related biomarkers in elderly patients with Alzheimer's disease [26]. In our study, we were unable to investigate the correlation between the severity of neurocognitive disorders and the severity of malnutrition due to the small sample size. However, Brocker et al. [11] were able to establish a correlation and found that malnourished patients had a significantly lower MMSE score ( $p$  value  $< 0.001$ ). Berlinger et al. [8] reported close correlations between weight loss, duration of illness, and cognitive status. All of our patients (100%) received CNO-based treatment with advice on food enrichment and meal splitting. None of our patients received enteral or parenteral nutrition. As suggested in the literature, we preferred to focus on oral feeding. For patients who refused to eat or who had food preferences, we recommended splitting meals and preparing meals according to their preferences. None of our patients' malnutrition required enteral or parenteral nutrition.

## 5. Conclusion

There is a close relationship between dementia and malnutrition. Clinical approaches to minimizing malnutrition in people with AD should include regular screening for malnutrition and its risk factors, avoidance of dietary restrictions, and support for people at risk of malnutrition with oral nutritional supplements. Educating caregivers and teaching them simple techniques for feeding patients properly is also a good way to prevent, or at least delay, the onset of malnutrition, which seems inevitable in this disease.

## Abbreviations

|     |                             |
|-----|-----------------------------|
| AD  | Alzheimer's Disease         |
| ADL | Activities of Daily Living  |
| CRP | C-reactive Protein          |
| GDS | Geriatric Depression Scale  |
| MNA | Mini Nutritional Assessment |

## Conflicts of Interest

The authors declare no conflicts of interest.

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